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William Arbuthnot Lane

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The Journal of Bone and Joint Surgery

EDITORIALS AND ANNOTATIONS

LEONARDO DA VINCI AND NICHOLAS ANDRY ON POSTURE

In the recent celebrations of the five hundredth anniversary of the birth of Leonardo da Vinci (Fig. 1) much has been said of his contributions to anatomy and to visceral physiology, but strangely little about posture—that common concern of artist, anatomist and physiologist.

Leonardo wrote: "The centre of gravity of a man who lifts one of his feet from the ground always rests on the centre of the sole of the foot [he stands on]. A man, in going upstairs, involuntarily throws so much weight forward and on the side of the upper foot as to be a counterpoise to the lower leg, so that the labour of his lower leg is limited to raising itself. . . . Observe the perpendicular line below the centre of gravity of the man" (Fig. 2).

"A man who is mounting any slope finds that he must involuntarily throw the most weight forward, on the higher foot, rather than behind—that is in front of the axis and not behind it. Hence a man will always, involuntarily, throw the greater weight towards the point whither he desires to move than in any other direction. The faster a man runs, the more he leans forwards towards the point he runs to and throws more weight in front of his axis than behind" (Fig. 3).

This last observation is well illustrated by the drawing from the Windsor collection of "A man pursuing a woman over a bridge (?)" (Clark 1935) (Fig. 4). The man's centre of gravity is farther in front of his leading foot than the woman's centre of gravity is in front of hers: consequently the man must be travelling faster, and so he will catch the woman.

Andry applied such principles in his enunciation of active correction—his greatest contribution to the art that he christened. His debt to Leonardo is acknowledged in the passage that follows, by an asterisk and the footnote "* Leonard da Vinci."

Andry wrote: ". . . if a Child inclines his Shoulder too much to the right Side, make him support himself upon the left Foot.

"Another method of managing a Child when he either raises or depresses one Shoulder too much, is to put some

FIG. 1

Leonardo da Vinci at about forty-five years of age. A drawing, possibly a self-portrait, from the Royal Collection (Clark).

By gracious permission of H.M. The Queen.

sort of Burthen upon the Shoulder that is lowest, and let the highest quite alone; for the weight upon the low Shoulder will oblige him to raise it up, and at the same time will make him depress the other.

"The Shoulder that carries a Burden rises always higher than that which is not loaded, and hence the central Line of all the Weight, both of the Body and the Burthen, passes through that Leg which sustains the Weight. If the Case was not so, the Body must tumble. But Nature has provided against this Inconveniency, by making an equal part of the Weight of

FIG. 2

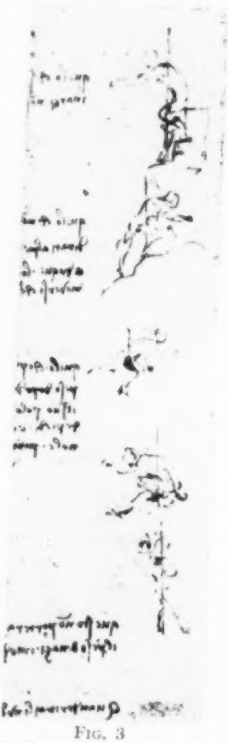

FIG. 3

Figure 2—Balance in going up a step. Drawings by Leonardo da Vinci in the Forster Library, South Kensington (Richter). Figure 3—The centre of gravity in mounting a slope and in running. The faster a man runs, the further is his centre of gravity in front of a vertical line through the foot taking weight. Drawings by Leonardo da Vinci in the Institut de France (Richter).

the Body to be thrown to the side opposite to that upon which the Burthen is laid, which makes the Equilibrium; so that the Body is thereby obliged to stoop so low on that side which is not loaded, till it bears an equal Share of the Weight that is upon the other side; whence it happens that the Shoulder which is loaded rises up, while the other which is free of the Burthen falls lower.

"This is the Mechanism which Nature makes use of upon this Occasion to relieve the Body.* A Mechanism which lets us see the Errour of those, who, to oblige a Child to keep down his Shoulder if it is too high, lay a Piece of Lead upon that Shoulder, imagining that this Weight will make him depress it, while, on the contrary, it is a means to make him raise it higher.

" Instead of laying a Weight upon the Shoulder which you would have raised, it may be sufficient to make the Child carry with that Hand something that is a little heavy, as a Straw Chair, . . . Or you may make him carry any heavy Thing under his Arm, as a large Book. . . . Another Method still, is to make him carry a little Ladder . . . The Shoulder which supports it will rise, and the other will fall lower. These little Ladders may be proportioned to the Age and Body of the Child, and it will be a Pleasure and Diversion for him to carry it " (Fig. 5).

It might even be conjectured that Andry's idea of the shouldered ladder came from one

FIG. 4
Man pursuing woman. Each pursues his (or her) centre of gravity; the man leans further forward than she does, and so must be travelling faster and will catch her. Drawing by Leonardo da Vinci in the Royal Collection (Richter, Clark).
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FIG. 5
Active correction of depressed shoulder in response to load (Andry).

of Leonardo's studies of labourers (Fig. 6). Almost certainly, however, Andry never laid eyes upon the furtive figure with the ladder. The folio comes from the Royal Collection of Leonardo's drawings in the Library of Windsor Castle. These drawings, numbering more than seven hundred, were bought for three and a half guineas early in 1690, or a little before, by King William III's secretary, Constantine Huygens. Soon afterwards he was protestingly taken from Kensington Palace by his Royal master to " le pays barbare d'Ireland," where the Battle of the Boyne was brewing. Nothing more seems to have been heard of the

FIG. 6

Figures of labourers, including a man with a ladder on his shoulder. Drawings by Leonardo da Vinci in the Royal Collection (Clark, MacCurdy).
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collection till it was discovered at that Palace in 1760, seventeen years after the English publication of Andry's book.

More than two centuries after Leonardo's death, his physiological observations on posture and balance were adapted and expanded by Andry in the treatment of postural defects by active correction. Two centuries later still his lessons are not yet fully learnt.

H. JACKSON BURROWS.

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RESEARCH FELLOWSHIP IN ORTHOPAEDIC SURGERY

Attention is drawn to the Research Fellowship in Orthopaedic Surgery with a renumeration of £4,500 which is now offered by the Royal College of Surgeons of England in memory of Laming Evans. Details are noted in later pages of the Journal.

"AVIATOR'S ASTRAGALUS"

W. D. COLTART, LONDON, ENGLAND

Formerly Wing Commander, Orthopaedic Specialist, Royal Air Force

The talus [astragalus] is less important as the keystone of an arch than as the chief component of a universal joint in the foot, and the crippling that may follow an injury to the bone is due to this mechanical importance.

The first account of an accident to the talus was made by Fabricius of Hilden in 1608, who wrote: "the Rev. Master Woolfbrand of Duisburg, a man strong and fleshy, in jumping from a bank three feet high so twisted and broke his right foot that the whole of the os tali was not only displaced but the ligaments by which it is bound to the other bones, being broken, it burst through the skin and hung out."

Sir Astley Cooper wrote at considerable length on fractures and dislocations of the talus, and since he published his "Surgical Essays" (1818) many surgeons here and abroad have referred to the subject in their works, but most refer to an experience of one or two cases and fill up space with many quotations from the literature. There is, however, an excellent account by Baudet in the *Revue de Chirurgie* of 1914, although he, like other earlier authors, has obviously been handicapped by a lack of good radiographs. Nowadays this difficulty does not exist and we gain a much clearer picture of the injuries that occur. Since 1914, although many descriptions have appeared in the American literature, accounts by British surgeons are few and I have been able to trace only those by Anderson (1919), Ollerenshaw (1921), Mercer (1928), Hosford (1932), Bonnin (1940) and McCurrich (1941). Again, these authors (except Anderson) refer to a clinical experience of one or two cases, and Miller and Baker (1939) stated: "In reviewing the literature of fracture and fracture-dislocations of the astragalus one finds many case reports but few recent long series of cases." The explanation lies in the rarity of the more severe and complicated injuries of the talus, so that surgeons, even those with a wide experience in accident surgery, cannot claim to have treated more than a few isolated cases. This lack of individual experience has meant a dearth of accurate description or classification in the medical literature and an absence of any real guidance on the treatment of accidents to the talus.

In 1919 Anderson, who was consulting surgeon to the Royal Flying Corps in the war of 1914–1918, described eighteen cases of fracture and dislocation of the talus. He was so impressed by the association of injuries of the talus with the aircraft crash that he named them collectively "Aviator's Astragalus." After remarking that falls from a height on to the foot are common in civilian occupations but that in those the calcaneum [os calcis] is usually broken, he proceeds: "On the other hand, the aviator usually falls with his machine and strikes the ground at an angle. The sole of the foot rests on the rudder bar and with the impact the latter gets pressed into the instep just in front of the heel. There the astragalus takes most of the force and becomes the seat of fracture. Before the actual fracture occurs, the foot may be in a position of acute dorsiflexion, plantar flexion, or may be inverted."

The clue provided by Anderson has been followed up in the last war and a large number of aviation injuries has provided the opportunity for a complete and fresh review of injuries of the talus.

CLINICAL MATERIAL

Between 1940 and 1945 approximately 25,000 fractures and dislocations were treated by surgeons working in orthopaedic units of the Royal Air Force. There were 228 injuries

to the talus—roughly 1 per cent of all injuries, or 6 per cent of 4,000 injuries affecting the ankle and foot. Survivors of air crashes seldom had bilateral injuries, only ten patients having injuries to each talus. The fact that 100 (43·8 per cent) of the injuries were sustained

TABLE I

CASES ADMITTED TO R.A.F. ORTHOPAEDIC CENTRES (1940–45)

Total number of fractures and dislocations		25,000
Total number of injuries to talus		228
Percentage of all injuries = 0·9		
Total number of fractures and dislocations of ankle and tarsus		4,000
Percentage of local injuries = 5·7		
Total number of patients with injuries to talus		218
Patients with unilateral injuries	208	
Patients with bilateral injuries of same type	3	
Patients with bilateral injuries of different type	7	

in accidents which had nothing to do with flying seems at first glance to belittle the significance of aviation in this condition, but if we consider only 154 serious injuries, leaving out the various chip and avulsion fractures and simple subtalar dislocations, we find that flying accidents accounted for 106, nearly 70 per cent of the more severe lesions, a figure that amply justifies Anderson's title of " Aviator's Astragalus " (Table I).

CLASSIFICATION

No previous account in the literature has included all the types of injury occurring in the present series, nor has any author hitherto described any injury of which examples have

TABLE II

CLASSIFICATION OF 228 INJURIES OF THE TALUS

Fractures	
Chip and avulsion fractures	56
Compression fractures of the head	6
Fractures of the body	15
Fractures of the neck	37
Fracture-dislocations	
Fracture of the body with subtalar dislocation	7
Fracture of the neck with subtalar dislocation	38
Fracture of neck with posterior dislocation of the body	31
Dislocations	
From ankle, subtalar and mid-tarsal joints	9
Miscellaneous injuries	11
Dislocation of tarsus at subtalar joint	18

not been found amongst this collection of 228 cases. For reasons that have already been mentioned, earlier classifications have been too scanty, including all types of injury as fractures of the neck, body or posterior process—too academic, such as that of Destot

(quoted by Baudet 1914)—or too complicated, as for example the classification included with an excellent account of a case of total dislocation by Bonnin (1940). With the advantage of a large, well documented series to study it was easily apparent that the injuries fell into three main categories—fractures, fracture-dislocations and total dislocations (Table II). There were inportant subdivisions to be made, particularly that between fractures of the neck of the talus with subtalar dislocation or subluxation of the tarsus, and fractures occurring at the same site but associated with complete posterior dislocation of the body of the talus from the ankle. A remarkable aspect of the subject is that, although the talus is as it were buried among the bones comprising the ankle and tarsus, it is nevertheless singled out for injury, whereas the other bones in the neighbourhood remain unaffected. There were, however, a few cases in which the talus shared in severe combined injuries to the local bones. These have been grouped together as " miscellaneous injuries " to avoid an over-detailed classification

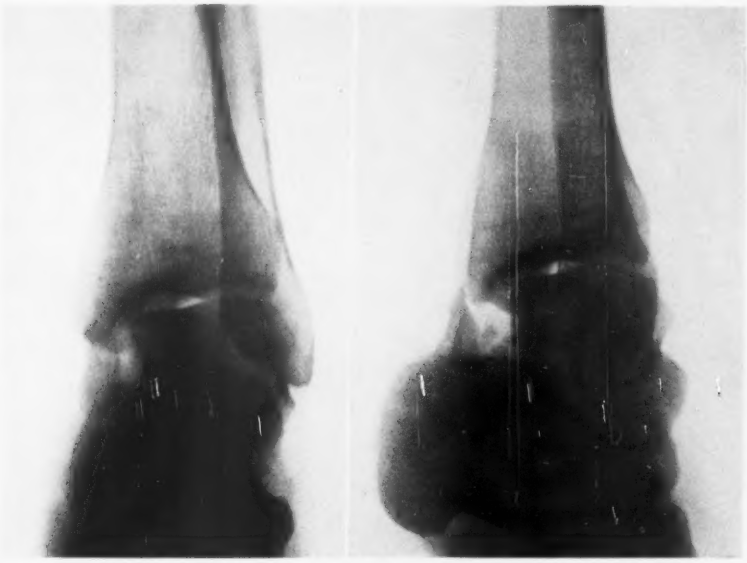

FIG. 1

Avulsion fracture of the talus. A large fragment is detached from the medial side of the bone.

(Table II). The disturbance of relationship in the subtalar joint is of considerable significance in the disablement which may follow injuries of the talus; because of this, subtalar dislocations have been included in the classification.

PATHOLOGICAL ANATOMY

Chip and avulsion fractures—In a twisting injury to the ankle, small fragments may be detached from the upper surface of the neck of the talus or from its medial and lateral walls. These may be regarded as minor complications of a " sprained ankle " and are revealed in the routine radiograph. Sometimes, however, a larger fragment, which includes part of the articular surface and the groove for the flexor longus hallucis tendon, is separated from the medial wall of the talus. The fragment is rotated and interferes with movement at the ankle. It is best removed by operation (Fig. 1).

Compression fractures of head of the talus—This injury is uncommon but characteristic. The radiographic appearances suggest that fracture is the result of a compression force

acting in the long axis of the foot. Four of the six cases occurred in flying accidents, and the position of full plantar-flexion with the foot stretched out against the rudder bar is one often assumed during efforts to prevent a crash. Radiographic diagnosis may be difficult unless

FIG. 2

Compression fracture of head of talus. The comminution is not easy to see.

FIG. 3

Compression fracture of head of talus, another type, with an associated fracture-dislocation of mid-tarsal joint.

there is a clear antero-posterior view of the foot. In the simpler injuries there is a contusion fracture of the head alone, but sometimes the forefoot is forcibly abducted, the mid-tarsal joint is dislocated and a large fragment is broken from the head of the talus (Figs. 2 and 3).

Fractures and fracture-dislocations of the neck of the talus—If the foot is forcibly extended at the ankle the talus is impacted against the anterior lip of the distal end of the tibia and a fracture occurs through the neck. In addition there may be radiographic evidence

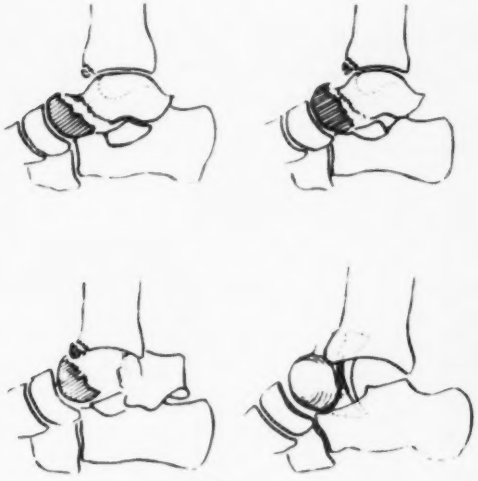

FIG. 4

FIG. 5

Figure 4—Diagrams showing the three types of injury produced by dorsiflexion and (bottom right) total dislocation, which is a plantar-flexion injury. Figure 5—Fracture of neck of talus. The effect of an impacting force can be seen in the neck of the talus and the lower end of the tibia.

FIG. 6

FIG. 7

Radiographs before (Fig. 6) and after (Fig. 7) reduction of a fracture of the neck of the talus with subtalar dislocation.

of damage to the contiguous margin of the tibia. This sort of violence is common in aviation accidents. If extension is forced still further, the line of stress may extend from the neck of the talus to the ligaments of the subtalar joint, which rupture, and the rest of the tarsus

subluxates forwards. In the final stage the body of the talus becomes dislocated backwards out of the ankle joint (Fig. 4).

It is easy, with the aid of radiographs, to distinguish between a fracture of the neck and a fracture-dislocation in which the body of the talus is displaced backwards out of the ankle joint; but it is important, although not so easy, to recognise those fractures of the neck of the talus which are complicated by subtalar dislocation. Examples are shown in Figures 5 and 6. In Figure 5 the effect of an impacting force can be seen in the neck of the talus and at the lower end of the tibia, but the contours of the subtalar joint remain unaffected and there is no displacement of the head of the talus on its neck. In contrast, Figure 6 shows a case in which the distal fragment of the talus has been displaced upwards and forwards with the rest of the tarsus; the proximal fragment has fallen into plantar flexion. As well as the

FIG. 8

FIG. 9

Figure 8—Fracture of neck of talus with complete medial dislocation of tarsus (pseudo-transverse fracture). Figure 9—The same case as Figure 8 after reduction, showing that this was not a "transverse" fracture of the body of the talus.

forward and upward displacement there is usually some medial, or less commonly lateral, displacement of the tarsus. In an extreme example there may be a fracture of the neck of the talus with a complete medial dislocation at the subtalar joint (Fig. 8). This injury has sometimes been described as a transverse fracture of the talus, but that is not its true nature, as can be seen from the radiograph taken after the dislocation had been reduced (Fig. 9).

Fractures and fracture-dislocations of the body of the talus—Figure 10 shows an injury in which the fracture line is approximately vertical and which appears at first glance to be another example of those fractures through the neck of the talus which have just been described. But the fracture line is through the upper articular surface, involves the ankle joint and is a fracture of the body of the talus. As in the case of fractures of the neck, this fracture of the body may be complicated by subtalar dislocation. The displacement is often more severe than when the fracture is through the neck of the talus (Fig. 11).

Severely comminuted fractures of the body are rare. There were but two cases in this series—one, the result of an aviation injury, is shown in Figure 12. In both cases the comminution was so severe that fusion of the ankle and subtalar joints was required. A

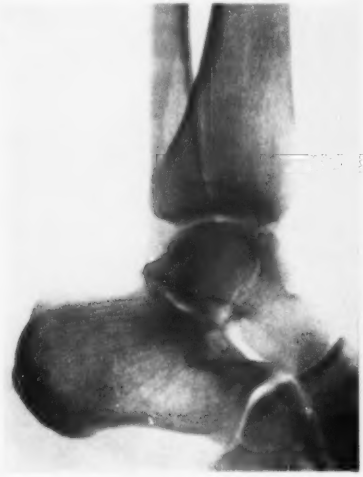

FIG. 10

FIG. 11

Figure 10—Vertical fracture through the body of the talus. Figure 11—Fracture of body of talus with subtalar displacement.

FIG. 12

FIG. 13

Comminuted compression fracture of the body of the talus. Figure 13—" Dome fracture " of the body of the talus.

fracture of the articular surface of the body of the type shown in Figure 13 may be described as a " dome fracture." The shape of the fragment is variable, but in a typical example the fragment was found to be upside down in the joint and was removed.

Fractures of neck of talus with posterior dislocation of the body—In many ways this is the most interesting of all injuries to the talus. In the thirty-one cases reviewed, one was caused by the unexpected detonation of a 4,000-lb. bomb, one by a motor cycle accident

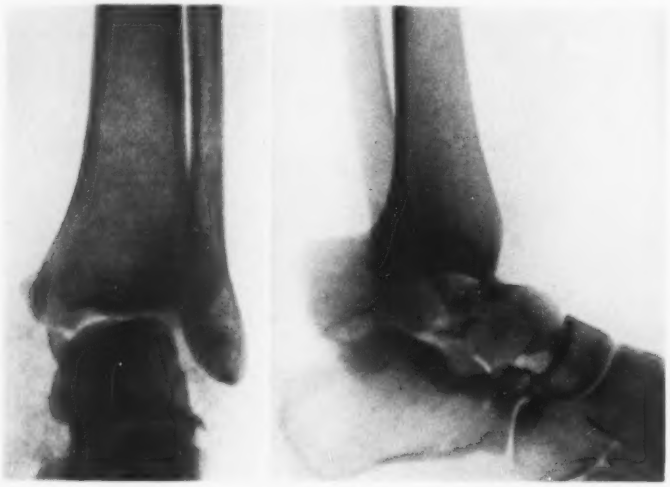

FIG. 14

Fracture of neck of talus, with posterior dislocation of the body. In this case the usual medial displacement has not occurred.

FIG. 15

Incomplete backward dislocation of the body of the talus.

and twenty-nine by aviation accidents. Descriptions of the typical clinical appearances had been made long before the invention of the flying machine, so that the injury is one which has occurred and still does from ordinary misfortune.

In a typical example (Fig. 14) the neck of the talus is fractured and the body, dislocated from ankle and subtalar joints, is displaced backwards on the upper surface of the calcaneum and is rotated through 90 degrees on its vertical axis so that the fractured surface points laterally. The whole body is usually displaced medially. In addition, the medial malleolus is fractured, but the lateral malleolus remains intact. In most cases this deformity is typical and constant. Occasionally backward dislocation of the talus is incomplete and the body remains unrotated and caught beneath the posterior articular margin of the tibia (Fig. 15). Rarely displacement is to the lateral side of the ankle.

Operation reveals that all the ligamentous and capsular attachments of the dislocated bone are torn off except those to the medial [deltoid] ligament, which may often be preserved. Injuries to the vessels, nerves and tendons at the medial side of the ankle are unusual despite the gross violence of the accident and the degree of displacement. This is probably because the body rotates away from them and, when it finally becomes displaced medially, remains behind the tendon of the flexor hallucis longus which protects the neurovascular bundle from harm.

FIG. 16
Total dislocation of the talus.

In about half the cases in this series the injury was compound and then the talus was visible in the wound or hanging out on the surface; in a few cases the fractured and dislocated body had been completely avulsed and was lost.

Total dislocation of the talus—In this injury the talus is dislocated from all three joints of which it forms a part. The characteristic feature is that displacement is forwards and laterally so that the bone comes to rest under the skin in front of the ankle on the dorso-lateral aspect of the foot. There was often complete avulsion of the talus, but the wound through which the extrusion had occurred was invariably in the same situation, in front of the ankle and to the lateral side.

Dislocation is the result of considerable violence. All nine instances in this review occurred in flying accidents. The domestic accidents which have been observed by others seem most often to occur in heavy men or women. Most cases—six out of nine reviewed here—were compound and the talus was removed. The typical displacement is shown in Figure 16. The talus has been dislocated forwards and laterally so that it lies in front of the lateral

FIG. 17

There has been a fracture-dislocation of the ankle combined with subtalar dislocation. As a result the talus is dislocated.

FIG. 18

Fracture through neck of talus with mid-tarsal fracture-dislocation.

malleolus and is rotated through 90 degrees in both its vertical and longitudinal axes, with the head pointing medially and the under-surface backwards. Probably this represents the greatest displacement, and rotation may not always be so complete in both directions. Occasionally the bone may be broken through its neck—but the injury is distinguished from other fracture-dislocations by displacement forwards instead of backwards.

Miscellaneous injuries—There were two cases in which fracture-dislocation of the ankle was combined with subtalar dislocation of the tarsus—so that the talus was left totally dislocated (Fig. 17). This injury is important because the talus may undergo avascular necrosis—which it will not do after either a Pott's fracture or subtalar dislocation alone.

In four cases a fracture through the neck of the talus was associated with dislocation at the mid-tarsal joint (Fig. 18). It will be observed that the line of fracture is oblique, with the fragment grossly displaced, and quite different from an ordinary vertical fracture of the neck.

FIG. 19

Combined comminuted fractures of talus and calcaneum.

Finally, there is an injury which appeared to be common as the result of the explosion of land-mines. This is a severe comminution of the calcaneum with a fracture through the neck of the talus (Fig. 19). The body of the talus is inverted and embedded in the calcaneum. The injury is usually compound and infected, and three of the five patients in this series suffered below-knee amputations.

Subtalar dislocation—This well known condition does not require further description here, but the radiographic appearances (Fig. 20) should be compared with those of fracture-dislocation, and especially total dislocation, of the talus.

DIAGNOSIS

Injuries of the talus are often the result of such a severe accident that the skin and soft tissues are burst and the bone in whole or part projects from the wound. Occasionally the talus is torn completely from its socket and lost, or may be found at some distance from

its owner. In these compound injuries a diagnosis is made by direct examination, but in closed injuries the patient presents a swollen, maybe deformed, ankle and foot. Swelling obscures minor displacements at the subtalar joint, which so frequently occur and which it is so important to recognise and reduce. Only by radiography can the true state of affairs be revealed. In ordinary dislocations of the tarsus at the subtalar joint, the head of the talus, uncovered by medial displacement of the navicular, is palpable beneath the skin on the dorsum of the foot; in total dislocation of the talus the whole bone presents under the skin in the same situation; and in fracture-dislocation, when the bone has been broken through its neck and the body has been displaced backwards from the ankle joint, this large posterior fragment may be felt as a bony hard mass between the medial malleolus and the tendo calcaneus [achillis].

FIG. 20
Subtalar dislocation of tarsus.

COMPLICATIONS

Wound infection—Often the more severe injuries are compound. Because of lacerations or swelling, suture of the skin is seldom possible and the wound is likely to become infected. The violence of the injury may have been sufficient to strip the talus of most of its soft tissue attachments; the blood supply to a large part of the bone becomes impaired and consequently resistance to infection is low. Once the talus itself becomes infected resolution is unlikely and removal of the bone as a sequestrum is usually necessary. Besides an actual wound there is another important source of infection. Reference has been made to protrusion of the talus beneath the skin in subtalar dislocation, total dislocation and posterior dislocation of the body. In these cases the skin is tightly stretched over the projecting bone, and sloughs rapidly unless tension is relieved by reduction of the deformity. The danger calls for an early diagnosis of the injury and for prompt action. Once the skin sloughs, infection spreads into

the deep tissues, and even if the talus itself is not involved, the resulting fibrosis militates against restoration of good function to the ankle and foot.

Avascular necrosis—The body of the talus, like the head of the femur and the proximal pole of the scaphoid bone, exhibits an aseptic form of bone necrosis under certain conditions of injury. This morbid change is recognised by increased opacity in the radiographs (Fig. 21). The blood supply to the talus, however, does not resemble that of the femoral head or of the proximal pole of the scaphoid. In these two the blood supply is, as it were, by a single channel which is severed by the fracture. Examination of a talus shows that it is well supplied with vascular foramina in three main groups: on the upper surface of the neck; in the sinus tarsi; and on the medial surface below the comma-shaped articular facet. This threefold supply does not protect the talus from the effect of those injuries which may destroy two-thirds or

FIG. 21

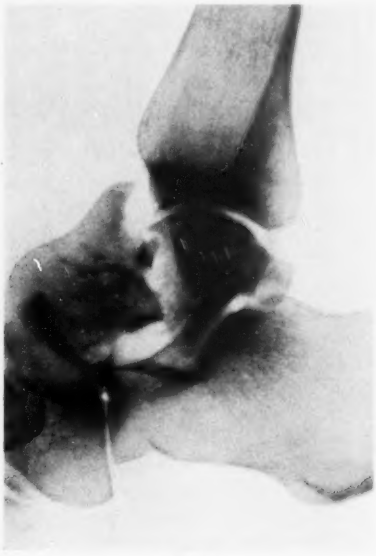

FIG. 22

Figure 21—Avascular necrosis. Well marked changes in the body of the talus ten weeks after a fracture-dislocation. Figure 22—" Apparent " avascular necrosis. Within a few hours of injury opacity of the body of the talus cannot be due to avascular changes. The apparent density is due to overshadowing by the fibular malleolus.

all of the vascular channels. Again differing from the neck of the femur and the carpal scaphoid, fractures of the neck and body of the talus unite without much difficulty, usually in about eight weeks; this rapid union is probably accounted for by the ease with which the fragments of a fractured talus may be immobilised. Allied to this observation is the further one that regeneration of the avascular body of the talus will take place, and proceed smoothly, under conservative treatment, to complete revascularisation, and this must be, anyhow partly, because the blood supply to the body is restored rapidly across the fracture of the neck.

Aseptic necrosis of the talus is not always easy to recognise. There is a tendency to diagnose the condition when it is not really present. This confusion arises because even in the normal foot a lateral radiograph must penetrate layers of denser cortical bone beneath the articular cartilage on the lateral malleolus, both sides of the talus and on the medial malleolus. Careful examination will distinguish between the diffuse avascular changes (Fig. 21)

and the localised apparent density (Fig. 22). If possible a film of the normal side, taken with the same exposure, should be available for comparison.

The incidence of avascular necrosis is shown in Table III. It occurred most frequently in the more severe injuries; in fact, with very few exceptions, in all those severe injuries in which the body of the talus had not been lost or removed. Since the talus receives its blood supply by three main channels we need not expect necrosis of the body if but one group of vessels is damaged. Necrosis did not occur after uncomplicated fracture of the neck, or after simple dislocation at the subtalar joint; in the former the blood supply is preserved through the

TABLE III

INCIDENCE OF AVASCULAR NECROSIS IN THE DIFFERENT TYPES OF INJURY

	Number of cases	Avascular necrosis	No avascular necrosis	Talus removed
Fracture neck of talus	37	—	37	—
Fracture body of talus	15	—	15	—
Fracture of body with subtalar dislocation	7	5	1	1
Fracture of neck with subtalar dislocation	38	12	26	—
Fracture of neck with dislocation of body	31	14	1	16
Total dislocations of talus	9	1	1	7
Subtalar dislocation	18	—	17	1
Miscellaneous	11	2	9	—

sinus tarsi and the medial ligament, and in the latter the vessels entering via the neck and the medial wall of the bone remain intact although those passing through the sinus tarsi may have been destroyed. Avascular necrosis was a complication in one-third of the cases of fracture of the neck with displacement at the subtalar joint. Possibly in those cases that escaped, the blood vessels entering through the sinus tarsi had remained intact. In a case of fracture with posterior dislocation that was examined at operation, the whole body of the talus had been denuded of soft tissue attachments, except for the medial ligament. In this instance avascular necrosis did not develop, so that evidently the blood supply through the medial ligament may be enough to preserve the vascularity of the whole body of the talus. This is not always so because, in four other cases in which a similar state of affairs was discovered, necrosis did subsequently develop. In the cases of avascular necrosis, a study of serial radiographs showed that the onset of the condition was always within eight weeks from the date of injury.

In fifteen cases conservative treatment was impossible because some operative reconstruction of the ankle or subtalar joint was required for an unreduced displacement. In the nineteen cases in which conservative treatment was feasible, regeneration of the necrotic bone occurred over periods varying between sixteen and thirty-four weeks. The average time required was twenty-four weeks, and this figure was not substantially affected whatever the type of injury or whether reduction had been achieved by operation or simple manipulation. The conservative method used was a below-knee plaster after reduction of the displacement. In some instances the patient was allowed to walk in plaster, but this made no difference and regeneration of the necrotic talus progressed satisfactorily. In all but two cases the plaster was retained until there was radiographic evidence of complete restitution of the normal bony texture. In the two cases in which plaster was discarded before this evidence had been obtained, the talus subsequently disintegrated and a painful arthritis of

the ankle ensued. Once regeneration of the bone has occurred, there are no later effects of the condition and the functional results achieved depended on the type of injury. A late follow-up of the cases of aseptic necrosis was attempted, but it was not informative because only three patients were traced. These reported that there had been no deterioration in the condition of their ankles two, three and five years after their discharge from medical care.

Arthritis of ankle or subtalar joint—In both fractures and fracture-dislocations, the violence may be enough to produce arthritis or ankylosis, even when deformity has been accurately reduced. The subtalar joint is most often involved. Quite slight degrees of displacement are enough to give rise to a painful arthritis which ultimately entails arthrodesis. It is, therefore, important to recognise displacement at this joint as a complication of what may appear to be merely a fracture of the neck of the talus unless the radiographs are inspected with great care.

Arthritis of the ankle is a less frequent complication. In some vertical fractures of the body of the talus there may be a residual step deformity which is very likely to lead to a painful arthritis. If the body of the talus is allowed to disintegrate as the result of avascular necrosis, arthritis is inevitable.

In these cases it is often a matter of great difficulty to decide whether the ankle or the subtalar joint is the source of pain. Sometimes both joints are involved and both may require surgical treatment.

MECHANISM OF INJURY

Aviation accidents were the commonest cause of serious fractures and fracture-dislocations of the talus, although not of all fractures, in the Royal Air Force. Figures taken from an earlier review of this subject demonstrate how often the talus was the site of injury in aviation accidents which involved the foot (Table IV). Injuries of the talus were more common than fracture of the calcaneum and occurred almost as often as fracture-dislocation of the ankle. This is because of the frequency with which forced dorsiflexion at the ankle occurs in an aircraft crash. However, not all serious injuries to the talus were caused in aeroplanes, and Baudet (1914) observed that a fall from a height could cause a fracture of the talus if the sole of the boot is flexible and if the victim lands so that the foot is forcibly extended at the ankle.

TABLE IV

FREQUENCY OF AIRCRAFT ACCIDENTS AS A CAUSE OF INJURIES IN THE REGION OF THE ANKLE

(R.A.F. cases 1940–42)

Injury	Aircraft accidents		Other accidents	
	number	per cent	number	per cent
Injuries of the talus . . .	53	70·7	22	29·3
Fracture of the calcaneum .	18	16	94	84
Fracture-dislocation of the ankle	60	27	162	73

He pointed out that it is not the strain of dorsiflexion which causes the fracture but the forcible impact of the margin of the tibia on the neck of the talus which produces what is in reality a crush fracture. Ombrédanne (1902), and more recently Gibson and Inkster (1934), have conducted experiments on the cadaver which showed that forced dorsiflexion will produce fractures of the neck of the talus and, if sufficient force is applied, backward dislocation of the body of the talus. Normally the talus is held in the ankle mortise by its own shape, assisted by the attachments of the neck and head, the talo-calcaneal ligaments, the strong posterior talo-fibular ligament, and the posterior and deep fibres of the medial ligament of

the ankle joint. In an accident dorsiflexion of the foot and impaction of the tibia against the neck of the talus occur together; the former ruptures ligaments and the latter fractures the neck. It seems probable that the various events occur in the following order. First, excessive dorsiflexion causes the wide anterior part of the body of the talus to become jammed in the mortise of the ankle joint. The posterior talo-calcaneal ligaments rupture. The neck of the talus is impacted against the tibia and is crushed. The calcaneum dislocates forwards, and possibly also medially or laterally if the foot is twisted into inversion or eversion. The body of the talus is pressed backwards by the approximation of the wedge-like lower end of the tibia to the calcaneum. The posterior talo-fibular ligament then ruptures, especially if the foot is inverted. Until this ligament tears, the body of the talus cannot escape backwards from the ankle joint. Once the ligament has torn and the body has begun to dislocate, it cannot avoid taking up a position on the supero-medial surface of the calcaneum, and rotating with its fractured anterior surface turned outwards. This position and rotation are compulsory because of the shape of the upper articular surface of the calcaneum and because of the torque exerted against the postero-medial surface of the talus by the long flexor tendon of the hallux.

There are three degrees of injury from dorsiflexion (see Fig. 4) and the lesion incurred will depend on the amount and duration of the force which is exerted—but the anatomical feature which determines whether or not the body of the talus will dislocate backwards is the integrity of the posterior talo-fibular ligament. Gibson and Inkster (1934) claimed that in their two experiments they were unable to rupture this ligament, but observation at six operations in this series confirmed that all attachments to the body were ruptured except the deep fibres of the medial ligaments, and Baudet has made the same observation.

Sometimes the fibular malleolus breaks instead of the ligament but this is unusual. The medial malleolus, however, is almost invariably fractured, and this suggests that it cannot be the pull of the medial ligament that rotates the talus.

It is probable that subtalar dislocation and total dislocation are produced by forcible plantar-flexion of the foot. Subtalar dislocations occur when the foot is off the ground—for instance, in kicking a football or in landing heavily on the foot from a jump. Passive plantar-flexion can occur only when the body weight is not resting on the sole of the foot, and it is forced plantar-flexion together with inversion which, in this case, ruptures the talo-calcaneal ligaments, and produces a subtalar dislocation.

Every total dislocation of the talus in this series was caused in an aircraft accident and the exact mechanism is difficult to determine, but descriptions of the injury in the literature give clear accounts of plantar-flexion and inversion of the foot in patients who sustained a similar injury in ordinary domestic accidents. It is suggested that in these cases plantar-flexion is so extreme that complete forward dislocation of the whole foot at the ankle first occurs. The foot is then forcibly adducted and inverted so that the talus is rotated through 90 degrees on its vertical and longitudinal axes; the foot itself then recoils below the tibia, but the talus is left displaced in its rotated position, outside and in front of the ankle joint.

Injuries of the talus can be classified, according to the mechanism of their production, into traction injuries—direct violence injuries—and those due to extension or to flexion at the ankle joint. It will be understood that dorsiflexion or plantar-flexion seldom occurs alone; inversion, eversion or adduction are associated displacing forces, except in fractures of the neck of the talus, which appear to be pure dorsiflexion injuries. Dorsiflexion in one group, and plantar-flexion in the other, are, however, the essential and principal elements in producing the more important injuries.

TREATMENT

Chip and avulsion fractures and compression fractures of the head of the talus—These injuries seldom need reduction and a short period of immobilisation in a walking plaster is all

that is required. Occasionally a detached fragment may need removal either because of its size and projection under the skin, or because it is blocking movement at the ankle or mid-tarsal joint.

Fractures and fracture-dislocations of the neck of the talus—In simple fractures displacement between the proximal and distal fragments is minimal and insignificant. No reduction is necessary; the fracture will unite without fail in six to eight weeks and the patient can spend the greater part of that time in a walking plaster. In contrast to simple fracture of the neck of the talus, fracture-dislocation requires very careful and accurate reduction, not so much on account of the obvious displacement at the neck, but because of subluxation at the subtalar joint. Reduction is easy enough, if the case is treated early. It being remembered that the proximal fragment is plantar-flexed, the foot is manipulated into full flexion so that the distal fragment is brought into alignment with the proximal; in addition any inward or outward displacement at the subtalar joint must be corrected.

FIG. 23

FIG. 24

Radiographs showing recurrence of deformity when the foot was brought up to a right angle four weeks after perfect reduction of a fracture-dislocation of the neck of the talus.

After reduction the foot can safely be immobilised in plaster in a position of equinus. This position is maintained for four weeks; the foot is then brought up to a right angle. At this stage the deformity may recur (Figs. 23 and 24).

Fractures and fracture-dislocations of the body of the talus—Comminuted fractures of the body are rare; when they occur the destruction is so considerable that fusion of the ankle and subtalar joint is advisable. Vertical fractures of the body may be complicated by talo-calcaneal displacement. Deformity can sometimes be overcome by manipulation with the foot plantar-flexed, as in fractures of the neck, but the displacement is usually severe, and complete reduction of both fracture and dislocation is difficult. The most usual end-result is a " step " deformity and subsequent arthritis of the ankle or subtalar joint, or of both (Fig. 25).

Out of forty-five examples of fracture of the neck or body of the talus complicated by subtalar displacement, there were only nine cases in which a good painless range of movement was restored to the foot, and in all these reduction had been perfect. In all other cases the

subtalar joint was painful, was ankylosed, or had been fused because of pain, and even this group included many cases in which there had been perfect reduction.

Fractures of neck with posterior dislocation of the body—More often than not this severe injury is compound and the body of the talus is avulsed and lost or has perforce to be removed because of gross comminution or soiling. However, the injuries are not all compound. It is sometimes possible to reduce the displacement by manipulation. The space between tibia and calcaneum is opened up by traction on the forefoot and heel, the foot is dorsiflexed and everted and then the body of the talus is twisted and pushed back into its place. An ingenious method of reduction was used by Armstrong, who exerted traction through the heel by means of a Kirschner wire and then manipulated the body of the talus into place after having transfixed it by a Steinmann's pin (Figs. 26, 27 and 28).

FIG. 25

"Step" deformity after a fracture through the body of the talus.

In closed injuries it is most important to relieve the pressure that the displaced talus exerts on the tightly stretched skin at the medial side of the foot. There should be no delay in resorting to operation if manipulation has failed to reduce the displacement. The bone is exposed through a curved incision directly over it, where it lies usually below and behind the medial malleolus. The neurovascular bundle and tendons are retracted out of danger, the ankle joint is widened by traction on the heel, and the talus rotated and manoeuvred into the ankle joint. Reduction is stable. Plaster is applied with the foot in a plantar-flexed position in order to restore the alignment of the head and body of the talus. It is important to relieve the dangerous pressure on the skin over the displaced bone when ordinary manipulation has failed but operative reduction is contra-indicated because of lack of facilities or because of the poor condition of the patient. In this event, the talus should be pushed into the soft tissue in the mid-line between the back of the ankle joint and the tendo calcaneus; there is plenty of room for it there and the tension on the skin will be relieved until operative reduction is feasible.

In this series the body of the talus was reduced by operation or manipulation in nine cases and the ultimate results have been satisfactory. In two other cases, although an open reduction was carried out operation could not be undertaken until some weeks after the injury and the body of the talus in each case had become markedly affected by avascular necrosis. The operation was completed by an arthrodesis of the ankle.

In the remaining twenty cases of this type of fracture-dislocation the body of the talus had either been avulsed at the time of the accident or was removed because of infection or as part of the toilet of a compound injury.

Total dislocation of the talus—Total dislocation of the talus presents a similar problem. The majority of the injuries are compound, but if not, relief of tension on the skin is just as urgent; here the talus cannot be displaced into some loose soft tissue area, and so must be reduced or removed at once if sloughing and infection are to be avoided. Manipulative reduction must be extremely difficult. There were two instances in which the procedure was carried out with success but unfortunately neither case was properly documented and it was not possible to discover what manoeuvres were used. Bonnin has reported a case in which the completely dislocated whole talus was reduced by operation, with good result.

Subtalar dislocation—The treatment of these comparatively frequent injuries calls for no special description here, except to draw attention once again to the danger of sloughing of the skin over the projecting head of the talus.

FIG. 26
Fracture-dislocation of talus before reduction.

FIG. 27

FIG. 28

The displacement was reduced by manipulation after transfixion of the body of the talus with a Steinmann's pin. (Mr J. R. Armstrong's case.)

The place of excision of the talus and arthrodesis in treatment—Some authors have recommended excision of the talus as the method of choice in the treatment of total dislocation or fracture-dislocation of the talus. There are cases, of course, in which there is no choice,

for the talus may be extruded and lost, it may be essential to remove a grossly damaged and soiled bone as part of the surgical treatment of a wound, or the talus may sequestrate in an infected compound injury, either primarily compound or when there has been necrosis of the skin over the displaced bone. However, in many cases the talus can be preserved with reasonable safety, provided some shred of soft tissue remains attached suggesting a possible blood supply—and often the attachments of the medial ligament do in fact remain. In this series excision of the talus never produced a painless mobile joint between tibia and calcaneum. Out of twenty-two cases of complete or partial excision, six could be regarded as "good" results because there was neither deformity nor pain and function was satisfactory, but in each case there was firm ankylosis between tibia and calcaneum. In other cases there was either so marked a deformity that a supporting steel and T-strap were necessary or there was a painful pseudarthrosis and bad function. These results should not be regarded as a condemnation of excision of the talus. In these cases the talus was removed after an injury to bone and soft tissues often in the presence of gross destruction and infection—all conditions

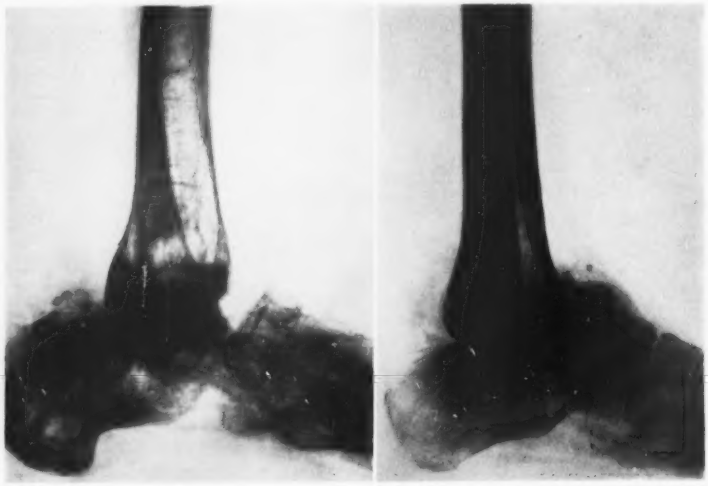

FIG. 29

Two examples of tibio-calcaneal fusion after removal of talus. The fusion is completed by fixing the fibular malleolus or a tibial graft to the lateral wall of the calcaneum.

which militate anywhere against a successful arthroplasty. Most recent opinions on the subject agree that excision of the talus fails in the treatment of fractures and dislocations of the talus. Good results have been reported, but it seems quite probable that the results refer only to function and not to mobility so that there may have been ankylosis between the tibia and calcaneum. If it is true that a better foot results after excision of the talus when the tibia becomes fully ankylosed to the calcaneum—and the observations made here suggest this—then there is an argument for deliberate operative fusion of the tibia to the foot as a secondary procedure in those cases in which the talus has been lost or removed.

It is surprising that the foot can remain so useful after complete obliteration of the ankle and subtalar joints. There were thirteen cases in which deliberate fusion of both joints was carried out either after loss of the talus, or because of traumatic arthritis of ankle and subtalar joints.

Talo-calcaneal fusion—Operation is carried out through a lateral incision which provides the exposure of the space between the tibia and calcaneum. The fibula is divided about two

inches above the ankle, and the distal fragment is removed. The under-surface of the tibia and the upper surface of the calcaneum are removed and the intervening space filled with chips of cancellous bone. A cortical bone graft is applied and fastened to the lateral surfaces of the tibia and calcaneum. The graft may be taken from the tibia or the removed portion of fibula may very easily be used (Fig. 29).

Tibio-talo-calcaneal fusion—Although the result—that is fusion of the tibia to the calcaneum—is the same whether the body of the talus is retained or not, with the talus still present the foot is of better shape, and some shortening is avoided. As before, the joints are exposed through a lateral incision. After removal of the remaining articular cartilage, fusion is completed with the aid of cancellous chips and a cortical graft from tibia or fibula (Fig. 30).

In both operations best results were obtained when the head of the talus was deliberately removed. It has been recommended that the head of the talus be preserved and fixed to the front of the tibia, but this tends to produce a varus deformity of the foot. The benefit of retaining the head of the talus to preserve the arch of an already disorganised foot seems doubtful.

FIG. 30

Tibio-talo-calcaneal fusion. The talus is retained in position and fusion is completed with the aid of a tibial graft and iliac chips.

Of the thirteen cases in which one or other of the fusion operations was carried out good functional results were obtained in all except one, in which bony anyklosis was defective. Each patient is walking more than two miles with ease, some can walk five miles and one still climbs mountains.

SUMMARY

1. Although fractures and dislocations of the talus have been described since 1608 the rarity of the more severe and complicated injuries has meant a dearth of accurate descriptions or classification in the literature.

2. A series of 228 injuries of the talus occurring in members of the Royal Air Force between 1940 and 1945 has been reviewed.

3. A simple but comprehensive classification of injuries of the talus is presented, together with a review of the pathological anatomy, clinical features, and methods of treatment. The importance of distinguishing between fractures and fracture-dislocations, and of watching carefully for displacements of the subtalar joint, is emphasised.

4. The important complications—infection, avascular necrosis and traumatic arthritis of the ankle or subtalar joint—are discussed. Infection may be the result of a compound injury, or may follow sloughing of the skin stretched over a displaced talus. Early reduction is, therefore, of great urgency in closed injuries. Avascular necrosis of the talus occurs in gross injuries when all or most of the soft-tissue attachments to the bone are severed. Revascularisation and regeneration will take place with patient conservative treatment.
5. The mechanism of injury is discussed.
6. The results of excision of the talus are poor. Every effort should be made to preserve the body of the talus, but if its loss is inevitable a useful foot can be regained by deliberate fusion of the tibia to the calcaneum.

I am grateful to the Medical Authorities of the Royal Air Force for their permission to use clinical material; to my colleagues who have allowed the study of cases that they have treated with such care and consequent success; and to Sir Reginald Watson-Jones for his inspiration.

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INFECTIONS OF THE HAND

A Review Based on 1,000 Consecutive Cases

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Infections of the hand are still very common, despite the increasing awareness of the importance of preventive measures. The introduction of antibiotics and a higher standard of surgery in these conditions have led to a change in the problem since the publication of the classical treatise by Kanavel (1925); and the neglected hands which he described and treated are now rarities. Within recent years several papers have been published from clinics especially concerned with the treatment of septic hands, and the methods advocated have varied from wide excision and suture of the infected area (Loudon, Miniero and Scott 1948) to a system of minimal intervention (Gordon 1951). It is clear that where interest and care are taken and a gentle technique followed, the results will be good. There are two problems in management. The first is to consider how to restore a patient with a simple infection to full earning capacity in the shortest time; and the second is to devise the best treatment for difficult and complicated conditions—notably infections involving bone, joint and tendon sheaths, and extensive sloughing of skin and subcutaneous tissues.

The purpose of this paper is to present the treatment and results of 1,000 consecutive cases from the hand clinic attached to the Surgical Department of the Royal Victoria Infirmary, Newcastle-upon-Tyne, and to seek to answer these problems.

The methods of treatment described do not depart from accepted surgical principles. These principles are discussed in general and also as applied to particular types of infection. The results are assessed in terms of "time to healing from first attendance" (henceforth referred to as the "healing time") and on the ultimate function and appearance. An attempt has been made to follow up all those cases in which a residual disability of any sort was anticipated. It has been stressed (Pilcher *et al.* 1948) that the important period to assess from the economic standpoint is the total disability period. While this is agreed, a simpler guide to the efficacy of treatment is in fact provided by the period elapsing between first attendance at the clinic and final healing, for patients in light occupations will be at work before the end of this period, whereas most of those engaged in mining and heavy engineering will be off work for a longer time.

For each patient, details noted have included the nature of any previous injury, the treatment before attendance at the clinic and the time interval and work lost before attendance. For every type of lesion a mean healing time can be found. When there is considerable delay in healing, the cause can usually be discovered in the previous history, in the complications existing when the hand is first seen, or in errors of treatment. A study of these factors has in some cases led to modifications in the method employed, and has also provided the data from which the probable result can be forecast when using a standard treatment for standard lesions. Particular emphasis will be given to the treatment of hands with skin necrosis and to the indications for skin grafting. In what follows there will first be a discussion of general matters followed by a more detailed report of groups of different infective lesions.

GENERAL CONSIDERATIONS

Organisation—All injuries and infections of the hand are seen and treated in the hand clinic, except minor lacerations and abrasions which are dealt with in the accident room,

and closed fractures which are treated in the fracture clinic. The number of patients seen averaged 125 each month; approximately half of these were cases of injury. Facilities for operative surgery and post-operative dressings are provided in the hospital. All patients are admitted after operation, the most serious cases to the hospital ward and the remainder (the large majority) to a hostel providing dormitory accommodation and staffed by male orderlies. In the hostel, rest of the part is assured and penicillin injections can be given regularly. By use of a hostel, accommodation and supervision are provided for patients with hand injuries and infections without wasting fully equipped hospital beds and trained staff; we believe that under these conditions wound healing and control of infection proceed more surely and the period during which the patient is off work is thereby shortened.

The patient—All the patients in this series were men or children, no facilities being available in the hostel for the treatment of women. The only patients who have been excluded are children under the age of six and patients who refused treatment. Twenty-five per cent of patients were engaged in some form of metal work or engineering and 13 per cent in unskilled labouring. It is interesting to note that whereas mining accounted for 35 per cent of serious injuries of the hand, it was responsible for only 13 per cent of infections. Twelve per cent of the patients were schoolboys.

Etiology—A history of injury was given by two-thirds of the patients and the time elapsing between the injury and the onset of infection averaged four days. Out of the whole 1,000 cases, only two—one of suppurative tenosynovitis and one of septic arthritis—resulted from the inadequate treatment of a serious primary injury. This serves to emphasise that it is not the serious injuries but the trivial ones—abrasions, pricks, splinters, minor blows, blisters—that give rise to infections. There was clearly an occupational trend, even in the absence of a definite history of trauma, for infections occurred mainly in men exposed to minor injuries, from such causes as metal filings. By contrast, in only nine patients were there suppurative lesions elsewhere in the body. The association with hand sepsis of skin and nasal carriage of the staphylococcus aureus has been described by Williams and Miles (1949). The present series tends to support the theory that these organisms enter through skin breaches which may pass unnoticed by the patient, or by way of sweat and sebaceous glands (Cole and Elman 1948). It seems unlikely that haematogenous infection plays a large part.

Previous history—Most of our patients came to the clinic when infection was established. The duration of symptoms before attendance, in the 857 cases for which information is

TABLE I

DURATION OF SYMPTOMS BEFORE ATTENDANCE AT HOSPITAL
(857 CASES)

Number of days before attendance	Number of cases	Per cent
0–2	176	20
3–4	300	35
5–7	245	29
8–70	136	16

available, is shown in Table I. The calculated mean period is six days, but it will be seen that most patients came for treatment after three days.

CLASSIFICATION OF INFECTIONS

The classification used is set out in Table II. It will be seen that some of the numbers given in the tables of results do not correspond with those listed in Table II. The reasons

TABLE II

CLASSIFICATION OF 1,000 CASES OF HAND INFECTION

Type of infection	Number of cases
Infection around the nail	233
Paronychia	
Acute	176
Chronic	31
Subungual infection	
Acute	25
Chronic	1
Infection of pulp space	244
Felon	
Simple	87
With skin necrosis	97
With osteitis	33
Apical infection	
Simple	17
With osteitis	10
Subcuticular infection	33
Subcutaneous infection	412
Middle compartment of finger	87
Proximal compartment of finger	110
Distal palm and web space	125
Proximal palm	47
Dorsum	43
Deep palmar space	6
Thenar	5
Mid-palmar	1
Primary tendon sheath infection	3
Joint infection	7
Acute	4
Subacute	3
Carbuncle	27
Cellulitis	24
Miscellaneous	11
Erysipeloid	1
Infected dermoid cyst	8
Infected papilloma	2
Total	1,000

for this are that notes taken at the beginning of the series were not always complete, and also that some of the patients defaulted before treatment was finished; some cases were therefore necessarily excluded from the tables of results.

PRINCIPLES OF TREATMENT

The place of antibiotics—The use of penicillin in the treatment of infections of the hand has been discussed by several authors (Bolton, Catchpole and Jepson 1947, Webster 1947, D'Abreu *et al.* 1947, Barclay 1949, Harrison *et al.* 1949). No attempt has been made in the present series to carry out any controlled investigation, but we believe that penicillin has three distinct uses: 1) It is employed to abort an early infection. Since many of these patients receive all their treatment from the general practitioner, the actual number of infections

successfully treated in this way is not known. 2) Penicillin helps to localise the infective process and to limit its spread once suppuration has occurred. Operation in the stage of cellulitis is contra-indicated. 3) Penicillin has radically altered the prognosis in severe infections of the hand involving bone, joint and tendon sheath. It is our custom in these cases, and also in others that are not responding rapidly to routine treatment, to test the organism for its antibiotic sensitivity. We have found that the predominant organism is the staphylococcus aureus, which in most cases is penicillin-sensitive. If, however, it is resistant to penicillin, but sensitive to another antibiotic, the appropriate drug is substituted. It is

FIG. 1

FIG. 2

FIG. 3

Photographs illustrating the advantages of skin grafting in cases of skin necrosis. Figure 1—Subcutaneous infection of the middle compartment of the finger. Cuticle raised by pus. Figure 2—Excision of the cuticle released underlying pus and revealed true skin necrosis. Figure 3—After removal of pus, intact tendon sheath and neurovascular bundles were seen.

FIG. 4

FIG. 5

FIG. 6

Figure 4—A granulating deficiency remained after the inflammation had subsided; this was grafted. Figures 5 and 6 show the satisfactory function regained.

our custom to give 100,000 units of penicillin in aqueous solution every six hours to patients in the hostel and, to the few who are being treated as out-patients, " Distaquaine " penicillin, 300,000 units daily.

The early case—Infections are not commonly seen at the clinic at a stage before suppuration has occurred, but if proper treatment is instituted within twenty-four hours of the onset of symptoms, resolution will often occur without the need for operative intervention. In the case of pulp space infection, the earliest symptom noticed by the patient is a sensation of

pricking and heat, which precedes the characteristic throbbing by several hours. At this stage, when there are usually no physical signs, the correct treatment consists of splinting the affected part, elevation in a sling and a course of systemic penicillin.

The established case—Most of our patients fall into this category and many aspects of their treatment are common to all. Severe infections of the hand, and those in which lymphangitis is marked, need rest in bed for a few days. In all cases local rest is required. The plentiful use of wool and careful bandaging provide adequate immobilisation, and splinting with plaster of Paris is reserved for infections of bone or joint. Pain and oedema are relieved by elevation of the hand on pillows when the patient is in bed, and in a sling when ambulant. The use of antibiotics has already been described. In uncomplicated infections a course of penicillin lasts three days, but this is extended in the case of bone and joint involvement. Surgery is carried out under full general anaesthesia, and a bloodless field, obtained by the use of a sphygmomanometer cuff, is essential, as are fine instruments and a gentle technique if further damage is to be avoided. Incisions are short and do not cross the flexion creases. In the presence of skin necrosis, classical incisions are abandoned in favour of operating through the devitalised skin (Figs. 1 and 2). By these methods the path of the infection and the extensions from its original site can be seen and followed, the lesion precisely defined, slough removed and drainage established, without danger of injury to adjacent structures (Fig. 3). The only form of drainage used is a strip of vaseline gauze sufficient to prevent the skin edges from closing prematurely. If the early post-operative course is satisfactory, dressings remain untouched for three days, patients being warned to keep them dry. Thereafter dressings are infrequent, and hot soaks and hypertonic applications are avoided. As soon as the infection is controlled, active exercises to restore function are begun. The assistance of a physiotherapist is seldom called upon.

The place of skin grafting—Even when skin necrosis has apparently been considerable, once the inflammatory oedema subsides the resulting skin loss is often slight and healing is rapid. Following control of the infection, in a small proportion of cases there remains a granulating defect, which is covered with a skin graft as soon as the area can be made sufficiently clean (Fig. 4). The penalty of allowing healing to take place by epithelialisation from the wound edges is often an adherent, painful scar, and a skin contracture which limits movement. Skin grafting promotes rapid healing and limits the formation of fibrous tissue.

In most cases a Thiersch graft suffices for skin cover, and the functional result of such a case is shown (Figs. 5 and 6); but if tendon or digital nerve is exposed, full thickness skin and a little subcutaneous tissue are needed. A simple and valuable method is to rotate a flap of skin from the side of the finger to cover the exposed area, a Thiersch graft being placed on the deficiency left by the flap. Skin grafting was performed in eleven patients in this series (Table III). In two of the eleven patients the result was unsatisfactory.

INDIVIDUAL LESIONS

INFECTION AROUND THE NAIL

Pathological changes—Acute paronychia begins as a subcuticular infection of the nail fold which later spreads round the side of the nail. It is distinguished from a subungual infection in which pus forms primarily under the nail itself, as a sequal to a haematoma or foreign body. Chronic paronychia commonly presents in one of two ways: 1) as a heap of granulation tissue appearing at the side of the nail; and 2) as a thin purulent discharge from the nail fold, often following an inadequately treated acute infection, especially when frequent wet dressings have been applied. Retained fragments of dead nail are a common cause. Only one chronic infection due to a fungus occurred in this series.

TABLE III

ELEVEN CASES IN WHICH SKIN GRAFTING WAS UNDERTAKEN

Case	Diagnosis	Delay before attending clinic (*days*)	Type of graft	Time between incision and grafting (*days*)	Total healing time (*days*)	Remarks
1	Chronic paronychia	14	Thiersch	14	30	No tenderness. Full movement
2	Pulp infection with sequestrum of terminal phalanx, destruction of tendon sheath and spread to dorsum	28	Thiersch	12	28	Slight tenderness. Full movement
3	Subcutaneous infection second compartment	4	Thiersch	8	22	No tenderness. Full movement
4	Subcutaneous infection second compartment	7	Thiersch	13	27	No tenderness. Full movement
5	Distal palmar abscess	5	Thiersch	17	31	No tenderness. Full movement
6	Carbuncle. Patient admitted in incipient diabetic coma	7	Thiersch	18	39	No tenderness. Full movement
7	Pulp infection (twice incised elsewhere), with destruction of tendon sheath	14	Cross finger flap	20	56	Slight tenderness. Movement restricted to 50% at middle and 25% at distal joints. Unsatisfactory result
8	Pulp infection extending to second compartment, with exposure of tendon and nerve	9	Rotation flap and Thiersch	14	38	No tenderness. 50% movement at distal joint. Full movement at middle joint
9	Subcutaneous infection second and first compartments, with exposure of tendon and nerve	2	Rotation flap and Thiersch	14	38	No tenderness. 50% movement at middle and distal joints.
10	Subcutaneous infection second compartment, with exposure of tendon	11	1. Thiersch 2. Rotation flap and Thiersch	1·21 2·33	70	Thiersch failed and finger healed with contracture. At second operation profundus tendon seen to have sloughed. Now has good skin cover but only sublimis movement. Unsatisfactory result
11	Subcutaneous infection second and first compartments	13	Cross arm flap	17	53	No tenderness. 50% sublimis movement only. This was a very late infection with sloughing tendons. Patient did not wish amputation and is pleased with result

Complications—The most frequent complication of an infection around the nail is extension to the pulp space through a sinus at the side of the nail bed. This occurred in twenty-four out of 176 cases of acute paronychia. Early infection of the terminal phalanx was found in four cases, the diagnosis being made on the palpation of rough bone, denuded of periosteum. In two adolescents the epiphysis was separated by pus, and in one of them the diaphysis

was lifted out at operation and pus was seen in the terminal joint. One case presented with widespread skin necrosis and healing was hastened by grafting.

Treatment—Once pus has formed, operative treatment is necessary. In most cases of acute paronychia a flap of skin is raised and the base of the nail is removed to afford adequate drainage. Less drastic procedures are seldom sufficient in hands hardened by heavy manual work. If pus is localised at the side of the nail, the abscess is saucerised by removal of a segment of nail and adjacent cuticle. Comparable treatment is applied to chronic infections, and any granulations are curetted. The whole nail is removed only if it is " floating," which is the rule in subungual infections. The treatment of complications follows the principles already described. Extension to the pulp space is drained through enlargement of the existing sinus and not by separate incision. If there is separation of the epiphysis from the diaphysis, the finger is immobilised in a plaster similar to that used for " mallet finger."

Results—The results of treatment, expressed in healing time, are given in Table IV. The finger in which the epiphysis became separated from the diaphysis healed in fifteen days and

TABLE IV

RESULTS OF TREATMENT IN INFECTIONS AROUND THE NAIL

Type of lesion	Number of cases	Average healing time in days
Paronychia		
Acute . .	152	9
Chronic .	23	13
Subungual		
Acute . .	23	8·5

full movement was restored in six weeks. The case with joint infection resolved without destruction of joint surfaces, and regeneration of the terminal phalanx took place with almost full movement at the distal joint. One case of acute paronychia took more than three weeks to heal. Pus had spread to the pulp space, which was drained by separate incision; this error may account for the delay.

INFECTIONS OF THE PULP SPACE

Pathological changes—A felon is an infection originating between the fibrous septa of the distal pulp space and spreading either outwards through the skin, inwards towards the bone of the terminal phalanx or laterally through the rest of the pulp. Its natural history has been described in detail by Bolton, Fowler and Jepson (1949). In two-thirds of our cases there was a definite history of injury which is assumed to have afforded the portal of entry. The felon is distinct from an abscess at the tip of the pulp beneath the distal portion of the nail, which has been termed an apical infection by Pilcher *et al.* (1948). Despite the greater incidence of bone infection due to the proximity of the terminal phalanx, the prognosis in this group with respect to healing time and ultimate function is much better than in other infections of the pulp space. In this series, cases of felon have been further sub-divided according to the presence of skin necrosis or osteitis.

Complications—Bone infection is the most important complication of pulp infections. Our criteria are the palpation of rough bone denuded of periosteum, the finding of a sequestrum at the original operation, or the presence or later development of bone erosion seen in the radiographs. The recognition of rough bone in the absence of gross destruction clinically or radiologically is of great importance, because adequate treatment will prevent the osteitis from becoming established. There were twelve such cases in this series. Of the twenty-one cases of established bone infection, fourteen showed gross destructive changes at the time of

operation, and seven developed osteitis during the course of treatment. All but one of these secondary infections occurred early in the series; it is probable that the causes were badly placed incisions.

Other complications seen on first attendance at the clinic were: spread under nail fold—eight cases; spread to dorsum—one case; spread to middle compartment—nine cases; destruction of tendon sheath—four cases; massive sloughing of pulp—five cases; widespread skin necrosis requiring grafting—three cases.

Treatment—By the time that most cases are seen an abscess has already become localised, and a skin sinus is often present. Incisions are not made in the stage of cellulitis, but penicillin and immobilisation are employed to assist localisation. The method of incision has not remained constant throughout this series. The general rule has been to use a " hockey-stick " incision for the simple felon, but to explore through the sinus if skin necrosis is present, a narrow ellipse of skin being excised to maintain drainage. Some bad results have been due to " through-and-through " incisions employed at the beginning of the series. Like many others interested in hand infections, we now tend to incise directly over the area of greatest tenderness. If doubt exists concerning localisation, it is wise to delay incision. Reference is made later to the effect on final function of the method of incision. Apical abscesses are " unroofed " by removing a small area of skin, together with a segment of nail.

Infection with osteitis is almost always accompanied by skin necrosis, and approach is made through the sinus. If a sequestrum is present it is lifted out, but in other respects the bone is not touched once the diagnosis has been made. The post-operative course of penicillin is extended to seven to fourteen days, according to the clinical response. Progress is usually arrested in the early case; in the established case it is our impression that healing proceeds more rapidly, but there is no proof of this. A second operation was performed for sequestrectomy in seven cases, and for removal of slough in one case.

Results—The results of treatment in the different varieties of pulp space infections are given in Table V.

TABLE V

RESULTS IN INFECTIONS OF THE PULP SPACE

Type of lesion	Number of cases	Average healing time in days
Felon		
Simple . .	77	10·5
With skin necrosis	88	15
With osteitis .	32	30
Apical infection		
Simple . .	14	7·5
With osteitis .	10	12

Opinions differ regarding the correct incision for infection of the pulp space. There is no doubt that the use of bilateral incisions in the pulp was the cause of delayed healing in several cases and this method was soon abandoned. We thought that it would be interesting to contrast the late results of the various incisions which were employed. The usual objection to an incision on the tactile part of the pulp is based on the claim that it may leave a tender scar where such is least desirable. " Hockey-stick " incisions also have been condemned on the grounds that they may produce a persistent painful state or an anaesthetic finger tip from digital nerve injury. With these objections in mind, we reviewed forty-one patients approximately six months after discharge from the clinic; cases complicated by osteitis were not included. Of sixteen patients with " hockey-stick " incisions one, a miner, complained of tenderness. He wore a finger stall at work, but none at home. Examination showed that

the incision had been placed too far forward. Two patients with transverse incisions made no complaint. Twenty-one cases had been drained through an area of skin necrosis in the pulp: of these, three had some tenderness in the scar with an area of anaesthesia distally, although the patients were satisfied with the results. Two cases had been treated by " hockey-stick " incisions as well as by exploration through a sinus. One of these complained of tender scars as well as anaesthesia distally. Undoubtedly these last were errors of treatment. The number of observations is small, but the findings suggest that wherever an incision is made tender scars will result in a few instances. There were no unsatisfactory results among the apical infections.

An attempt was made to review all cases of felon with osteitis and twenty of the thirty-three patients were traced. Two patients who had had early bone infection now made no complaint. Of the eighteen patients who had had established bone infections, only three were completely satisfied. The complaints of the others were: ugly appearance of scar—four cases; marked wasting and deformity of pulp—seven cases; tenderness in the scar—six cases; poor sensation—three cases; more than 25 per cent limitation of movement at terminal joint—five cases; subsequent amputation—one case. It should be observed that in most of these cases there were other complications (such as massive sloughing of the pulp or local invasion of the tendon sheath) in addition to bone infection, but one must conclude that many advanced cases of this sort will be left with some measure of disability. In order to improve the results, attention should be directed to arresting the progress of infection in the early case.

SUBCUTICULAR INFECTION

Subcuticular infection occurs beneath the epidermis, the dermis remaining intact. Clinically, it can be distinguished from a " collar-stud " abscess by the absence of diffuse tenderness beyond the area of subcuticular pus. A blister is the common mode of origin.

Most cases can be treated without anaesthetic. The roof of the blister is removed with scissors, pus wiped away and the base inspected for a breach in its surface. If no extension is found, the surface is dusted with penicillin-lactose powder and a vaseline gauze dressing applied. In this series, the average healing time was six and a half days.

SUBCUTANEOUS INFECTION

It is convenient to group together all infections that occur at a subcutaneous level, because the natural history is similar in them all, the principles of treatment are the same, and the results are comparable. The distal pulp space presents a different problem in management and is therefore considered separately.

Pathological changes—In the fingers a minor penetrating wound commonly affords the portal of entry. In the palm and web space a subcuticular infection usually precedes a deeper extension, the hard overlying cuticle being more resistant to pressure necrosis than is the underlying dermis. Complex palmar abscesses are seen in which pus has spread in and through the palmar fascia, but not deep to the flexor tendons. These abscesses should not be mistaken for infections of the mid-palmar space.

Dorsal subcutaneous infections are seen more frequently in the fingers than in the hand, and are more varied in their pathology. Uncommon lesions occur on the knuckle pads and may involve the extensor tendon. Slaughtermen develop a chronic staphylococcal infection in which multiple indurated inflammatory swellings occur over the dorsal aspects of the proximal interphalangeal joints. The lesions contain sero-pus and are surrounded by a circumscribed area of oedema.

Complications—Skin necrosis is the commonest complication of subcutaneous infection, and details of the cases which were grafted have already been given. Spread of infection is frequent between adjacent compartments, or from the finger into the web space or subcutaneous

tissues of the palm. Involvement of deeper structures is not common, but when it occurs in a neglected case the result may be serious. The complications seen on first attendance at the clinic were: spread to pulp space—five cases; destruction of tendon sheath—seven cases; sloughing of profundus tendon—two cases; osteitis—one case; spread to bone, joint and tendon—one case; sloughing of palmar fascia—two cases; spreading lymphangitis—two cases. Two of these patients required amputation of the finger. Most of the complications were

TABLE VI

RESULTS IN SUBCUTANEOUS INFECTIONS

	Number of cases	Average healing time in days
Middle compartment of finger	81	16
Proximal compartment of finger	102	10
Distal palm and web space	113	12
Proximal palm	36	11·5
Dorsum	38	12

the direct result of pressure from pus under tension. When the tendon sheath was involved, and even in those cases in which the tendon itself had sloughed, pus was not found in the proximal portion of the sheath, in marked contra-distinction from a primary tendon sheath infection.

Treatment—Treatment follows the principles already described. When the skin is intact, short antero-lateral incisions are made in the fingers. In the distal palm, either a short transverse incision is made at the base of the finger, or the appropriate web is split longitudinally. For the first web space the curved edge of the first dorsal interosseous muscle provides a guide to the line of incision. When there is skin necrosis the abscess is approached through the area of devitalised skin. If part of the tendon sheath has been destroyed, penicillin solution is instilled into the sheath and the finger immobilised until the infection is controlled. The usual routine is adopted post-operatively.

Results—The results, expressed in healing time, are summarised in Table VI. It will be seen that the healing time was longer for infection of the middle compartment than in the other

TABLE VII

EFFECT OF SKIN NECROSIS ON HEALING TIME

Degree of skin necrosis	None	Slight	Considerable
Number of cases of subcutaneous infections of fingers, palm and web space	135	151	16
Average healing time in days	11	10·5	23

situations. Most of the complications occurred in this group, and if thirteen complicated cases are excluded, the healing time becomes twelve and a half days and approximates to the other subdivisions.

The degree of skin necrosis has an obvious influence on healing time. When the skin was viable the average healing time was eleven days; when there was " minimal skin necrosis " (that is, a skin sinus such as is found in a collar stud abscess or infection pointing in a

skin crease) the healing time was not affected, but when "considerable skin necrosis" was found—although not sufficient to demand skin grafting—the healing time was more than doubled (Table VII). Nevertheless in eight patients with uncomplicated infections, healing took over four weeks. In three of these there was delayed separation of slough, and in one case in which the whole of the dorsum of the hand was involved a serous discharge persisted because drainage was inadequate. In the remaining four cases no cause could be determined. The late results of uncomplicated cases with respect to appearance and function were good.

INFECTION OF THE DEEP PALMAR SPACES

Pathological changes—Deep palmar infections are now uncommon conditions. At operation the diagnosis of a thenar space infection is confirmed by seeing the deep extension of pus anterior to the adductor pollicis muscle; and of a mid-palmar space infection by seeing an abscess deep to the flexor tendons in the palm. Unless strict criteria are taken, an extensive infection of the first web space or complex subcutaneous palmar abscess may be mistaken for infection of the thenar or mid-palmar spaces respectively.

In this series the mode of origin of the thenar space infections was by direct implantation from a penetrating wound. The single instance of mid-palmar abscess arose as an extension from the fourth web space along the lumbrical canal.

Treatment—At operation the thenar space is approached by the same route as the first web space, namely by following the curved edge of the first dorsal interosseous muscle. If necessary a dorsal counter-incision can be made parallel to the second metacarpal. The mid-palmar abscess was drained through the fourth web.

Results—The results of these cases have been good. In the five cases of thenar space infection the average healing time was thirteen days. The mid-palmar abscess was healed in twelve days. Five of the patients have been reviewed; all showed a fully mobile hand with a linear scar and no tenderness.

TENDON SHEATH INFECTION

As primary thecal infection is considered to arise from what must be a common injury to those parts of the finger where the tendon sheath is superficial, it is surprising that only three cases were seen in this series, and one of these was not typical. Those cases in which the tendon sheath was involved secondarily from a late subcutaneous infection are not included in this group, but are classed as complications of the primary infection. The following are details of the three cases of primary thecal infection. The first patient had undergone a previous operation elsewhere and pus was found subcutaneously and in the tendon sheath. The sheath was opened and the proximal compartment irrigated with penicillin. Healing was complete in twenty-one days and subsequent examination showed full movement of the finger. The second patient was seen within twenty-four hours of the onset of symptoms. He had a severe general toxaemia and acute tenderness over the proximal compartments of the ulnar bursa, but without evidence of suppuration. He was treated by rest and intensive chemotherapy and never underwent operation. The diagnosis in retrospect was that of haematogenous ulnar bursitis. A year later he had a slight hyperextension deformity of the middle three digits, similar to that seen in paralysis of the intrinsic muscles, and these fingers lacked 40 degrees of extension at the proximal and 10 degrees at the distal interphalangeal joints. The third case was seen four days after a crush injury to the left index finger had been sutured elsewhere without exploration of the wound. There was moderately severe necrosis of the skin and subcutaneous tissues at the level of the middle digital skin crease, and pus exuded from the tendon sheath on applying pressure over its palmar extension. The sheath was approached through the necrotic tissue and penicillin instilled through a transverse palmar incision over the proximal cul-de-sac. Six months later full movement

was present at the metacarpo-phalangeal joint, 15 degrees of movement at the proximal and 20 degrees at the distal interphalangeal joint. Fixation was the direct result of infection in the sheath, but some improvement is still taking place.

JOINT INFECTION

Seven cases of primary septic arthritis were seen in this series, four of which were acute. Of the latter, two patients gave a clear history of previous trauma, and in three there was a skin sinus communicating with the joint. At operation intact articular cartilage was present in only one case and in this a mobile joint was preserved. In the other three patients destruction of the joint surfaces was clearly seen radiologically: the thumb was affected in each instance. In the first case an attempt was made to preserve an intact joint, with the result that suppuration continued and three operations were necessary. Nine months later there was a pseudarthrosis with a little pain, but the patient had resumed work as a joiner.

In the succeeding two cases a more radical primary operation was attempted with better results, and it is thought that this is the correct procedure for the established case. The joint is widely exposed and pus, débris, loose articular cartilage and projecting fragments of bone are removed. Penicillin solution is instilled into the cavity, the skin edges approximated and the joint immobilised in plaster of Paris. Both patients were aged sixty-five and have developed a painless pseudarthrosis with remarkably good function in the thumb. In younger men it would probably be wiser to obtain ankylosis.

Three cases of joint infection were subacute. When they were first seen there was widespread oedema and cellulitis of the hand but, after treatment by immobilisation and penicillin, tenderness became localised to a metacarpo-phalangeal joint, and all subsided without operation, though one developed osteoporosis around the affected joint, recalcification occurring later. In contrast to most infections of the hand, it seems likely that some cases of septic arthritis are haematogenous in origin. Focal sepsis was present in two of these patients, and one made a dramatic improvement after extraction of infected teeth.

CARBUNCLE

Carbuncle occurs on those parts of the dorsum of the hand which bear hair follicles. The only complications seen in this series were in two patients who developed spreading lymphangitis.

Initial treatment consists in systemic penicillin and immobilisation. The roofs of subcuticular abscesses are removed, and hypertonic dressings are used later to assist the separation of slough. At the beginning of the series several carbuncles were incised, but incision is now reserved for cases in which pus is pocketing subcutaneously.

In this series, the average healing time was fifteen days, but this includes one case in which it was thirty-nine days. The patient was admitted with incipient diabetic coma and a carbuncle occupying the radial half of the dorsum of the hand. After separation of slough a large crater was left, which was healed by skin grafting.

CELLULITIS

This group comprises infected injuries of the dorsum of the hand in which neither localisation nor suppuration occurs. In two patients a marked general toxaemia was of greater importance than the local infection of the hand. There was one case of human bite in which the patient made an uncomplicated recovery.

Treatment consists in local rest and systemic penicillin. The average healing time was eight and a half days. In one case it was prolonged to four weeks, after an attempt at secondary suture.

MISCELLANEOUS

One case of erysipeloid infection, occurring in a fish salesman, was treated with penicillin and cured in eight days. Eight cases of infected dermoid cyst were treated by removal of the cyst at the same time as drainage of the abscess. The average healing time was eleven days. Two cases of infected papillomata call for no especial comment.

DISCUSSION

It is not suggested that this account describes the only methods of treatment for infections of the hand, but that these methods give satisfactory results. At the outset, it was recalled that there were two aspects of the problem. The first was to consider how to restore a patient with a simple infection to full earning capacity in the shortest time, and the second how best to treat difficult and complicated conditions.

Our treatment of simple infections is founded on early drainage of pus under general anaesthesia and the use of a bloodless field; it embraces rest for the inflamed tissues, a short, intensive course of penicillin, and avoidance of secondary infection by the use of dry post-operative dressings which are changed infrequently. The accommodation provided by the hostel is a useful, though not an essential, adjunct. We consider that the methods are consistent in principle, and suitable for undergraduate teaching. An attempt has been made to standardise the treatment, and the measure of success obtained—expressed in healing time—indicates its value.

In our practice there is no doubt that the most frequent serious complications are bone infection accompanying abscesses of the pulp space, and subcutaneous infections which have progressed to widespread necrosis of the skin and subcutaneous tissues. By comparison, the classical infections of tendon sheath and deep palmar spaces are rare. Skin grafting has been given prominence because the result of its use in " salvage cases " has usually justified the trouble taken. We have found no simple answer to the problem of established bone infection, which remains a cause for dissatisfaction, but recognition of the early case should enable the progress of infection to be arrested.

No comparison has been made with other recently published reports because the criteria used are not the same, although several accounts show no wide divergence of views. We find it difficult, however, to agree with Gordon (1951) that the method of minimal interference, which may be safe in his hands, is suitable for practice anywhere outside a specialist clinic. Without a clear understanding of the pathology of hand sepsis and the opportunity for observation of many cases, delay must often lead to disaster. The excellent results obtained by Scott and his associates (1948) by the method of excision and suture suggest that this management has a place in the treatment of infections of the hand, but it seems unlikely that the technique could be applied to the many cases in our series in which skin necrosis of varying degree was present. This method too may be more appropriate in the specialist clinic, and may have its most useful application in the treatment of infections of joint and tendon sheath.

SUMMARY

1. A report is made of 1000 consecutive cases of infection of the hand treated in the hand clinic of the Surgical Department of the Royal Victoria Infirmary, Newcastle-upon-Tyne.

2. Standard lesions are given a standard treatment. The methods of treatment are described and the results are expressed according to the time to healing from first attendance at the clinic. An attempt was made to review those cases in which a disability of any sort was anticipated, and an assessment made with regard to appearance and function.

3. Many patients came to hospital at a late stage when skin necrosis had already occurred, and particular attention is paid to the management of this complication.

4. It is concluded that the principles of conservative surgery applied to the treatment of infected hands give good results.

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RESULTS OF TREATMENT OF INFECTIONS OF THE HAND

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A preliminary report on a method of treatment of infections of the hand was published from this Unit (Loudon, Mineiro and Scott, 1948). It was emphasised at that time that this was a small series of cases treated by the authors and that a report on a larger series would be published in due course. The essentials of the method were excision of all devitalised tissues and suture of the wound, plaster protection and immobilisation, parenteral penicillin and infrequent dressings. It was not suggested that this method was the answer to all types and stages of hand infection. It was pointed out that it was possible to obtain primary healing in a high proportion of hand infections if certain conditions were carefully observed and that this was a new observation in relation to these infections which was worthy of further consideration.

CLINICAL MATERIAL

We have now reviewed the records of 1,211 patients treated for hand infections from July 1948 to April 1951; of these, 145 resolved with conservative treatment and 1,066 required operation. For purposes of analysis it has been necessary to exclude 195 cases because the notes were inadequate in respect of treatment or follow up. The patients included in this series were dealt with throughout by all the members of the staff of the Accident Service and the routine followed was the same as for all other patients. They were seen and dealt with for the most part by the house surgeons to the Accident Service under the supervision of the senior residents and the consultant staff. The interest of the residents in this subject and their proficiency in dealing with it was stimulated in every possible way and it was impressed upon them that advice was available and should be sought whenever they were in doubt. As well as the general daily clinic a special septic hand clinic was held weekly to see any patient whose progress was not satisfactory. In about two-thirds, excision and suture were carried out; in the remainder other methods were considered more suitable by the person doing the operation. It is therefore not possible to compare the results obtained by different methods.

Our chief interest is in those in which primary healing was obtained; and in those in which it was not, the reasons for the failures and any complications which arose. The criterion adopted of success or failure is whether or not primary healing was obtained. An arbitrary figure for primary healing has been taken as seventeen days or less. This was done chiefly for two reasons. In no case in which there was any breakdown of the wound and discharge of pus did healing take place within seventeen days. With infrequent dressings there was, in a proportion of cases, a tendency to remove the sutures at the tenth day, apply a dry dressing, advise activity and see the patient again in a week. When there was any doubt about the completeness of healing on the tenth day, the case would be included as having healed (per primam) in seventeen days.

The healing time must be related as closely as possible to the severity of infection. Because of different descriptive methods and terminology it is difficult to describe " severity " in words which will be interpreted in the same way by all readers. The " degree " method, previously described, has obvious faults but we use it here because we believe it to be as reliable as any other method. First degree means no pus found; second—pus localised and confined to one space; third—pus extended from original site into other tissues; and fourth—discharging sinus.

Table I shows the proportion of the different types of infection which make up the total. In all groups except paronychia the cases have been divided into those which healed per primam and those which did not, and the relevant figures with regard to healing time and degree of infection have been analysed.

TABLE I

TYPE OF INFECTION

Palmar infection of fingers		**413**
Distal pulp	285	
Middle pulp	54	
Proximal pulp	74	
Dorsal infection of fingers and hand		**58**
Palmar infections		**109**
Distal palmar pulp	76	
Subcutaneous	16	
Thenar space	13	
Mid-palmar space	4	
Tendon sheath infections		**16**
Paronychia		**263**

RESULTS

Palmar infections of fingers (Table II)—If the palmar infections of the fingers are grouped together we find that, of 347 treated by excision and suture, 56 per cent healed by first intention in an average of just over eleven days, and that 43 per cent failed to do so and took an average of thirty-three days to heal: there was bone involvement in twenty cases, in five of which sequestrum formation occurred.

TABLE II

PALMAR INFECTIONS OF THE FINGERS

Site of infection	Number of cases	Primary healing		No primary healing	
		Number	Per cent	Number	Per cent
Distal pulp	226	133		93	
Middle pulp	50	24		26	
Proximal pulp	71	39		32	
Total	347	196	56·5	151	43·5
		Average healing time, 11·4 days		Average healing time, 34·3 days	
Degree of infection		Primary healing		No primary healing	
First degree		9·2 per cent		—	
Second degree		51·1 per cent		23·8 per cent	
Third degree		20·4 per cent		26·5 per cent	
Fourth degree		17·3 per cent		49·7 per cent	

In these 347 patients there were 362 operations and two dressings under anaesthesia in children. There were second operations in 4·3 per cent—of the fifteen second operations eight were skin grafts and seven were needed to improve drainage or remove a sequestrum. Two per cent of the patients required a second operation before effective drainage was achieved. There were three instances of damage to the neurovascular bundle, two definite and one doubtful. Twenty-six patients were admitted to hospital.

Dorsal infections of fingers and hand (Table III)—There were fifty-eight dorsal infections of fingers and hands, and forty-seven of these were treated by excision and suture. Fifty-one per cent healed by first intention, and second operations were required in five patients, four of them being for skin grafts. There were no other complications. Six patients were admitted to hospital.

TABLE III

DORSAL INFECTIONS OF FINGERS AND HAND

Number of cases	Primary healing		No primary healing	
	Number	per cent	Number	Per cent
47	24	51	23	49
	Average healing time, 13·5 days		Average healing time, 29·9 days	
Degree of infection	Primary healing (cases)		No primary healing (cases)	
First degree .	1		—	
Second degree .	9		2	
Third degree .	7		11	
Fourth degree .	7		10	

Infections of palm (Table IV)—There were 119 infections of the palm, and ninety-six of them were treated by excision and suture. Fifty-two per cent of these healed by first intention. A second operation was required in four patients, but not because of failure to produce effective drainage. It is interesting that only about one-sixth of these infections were fourth degree as compared with one-third in the case of finger pulp infections. This

TABLE IV

INFECTIONS OF THE PALM

Site of infection	Number of cases	Primary healing		No primary healing	
		Number	Per cent	Number	Per cent
Distal palmar pulp	70	37		33	
Subcutaneous .	13	6		7	
Thenar space .	10	5		5	
Mid-palmar space.	3	2		1	
Hypothenar space	—	—		—	
Total . .	96	50	52	46	48
		Average healing time, 11·9 days		Average healing time, 31·1 days	
Degree of infection		Primary healing (cases)		No primary healing (cases)	
First degree		2		—	
Second degree . . .		22		18	
Third degree		17		13	
Fourth degree . . .		9		15	

may be because the thick palmar skin does not break down to form a sinus but rather forces the infection to spread. It was found that when long transverse incisions were used there was a tendency for them to open up if mobilised early. Damage occurred to three neurovascular bundles. Twenty-seven patients were admitted to hospital.

Tendon sheath infections—There were sixteen patients with tendon sheath infection, ten being secondary to other finger infections (five of which had discharging sinuses) and five due to wounds or bites. One was a primary sheath infection. Six healed per primam in an average of 13·6 days and in five of them good function resulted. Of the other ten, eight healed in an average time of 36·5 days; three of these regained good function, in two it was fair, in two poor and in one unknown. Two fingers were amputated, one after healing and the other (with a multiple space infection extending to the tendon sheath) on the eighteenth day. In the whole series there were three other amputations—two for stiff fingers after multiple pulp space infections and one immediate amputation of the fifth finger for a very late and extensive infection. It was noted in a considerable proportion of third and fourth degree infections that the pus was tracking along the neurovascular bundle.

TABLE V

PARONYCHIA

Treatment	Number of cases	Average healing time
Usual incisions . . .	138	13·3 days
Usual incisions plus suture	93	13·1 days
Removal of nail only .	32	16·6 days
Total . . .	263	

Paronychia (Table V)—The only way in which our method of treatment of paronychia differs from those usually adopted is that an attempt is made to excise devitalised tissue and that when this is possible the incisions are sutured. This suture has some value in preventing retraction of scars at the base of the nail and the excision in assisting the growth of the new nail by providing early elimination of infected material. The results are shown in Table V.

CAUSES OF FAILURE

These can be classified into two groups: those in which there was trouble with the skin, and those in which excision was inadequate or infection led to further death of tissue.

Skin troubles arise from two sources—the first and most frequent is the presence before operation of dead skin with or without a sinus. The procedure has been to excise the sinus, thereby placing some tension on this part of the wound leading to separation of the edges and a small granulating area. The inclusion of the sinus in the incision sometimes required modification of accepted incisions. These modified incisions frequently produced trouble. The estimation of death of skin around a sinus is not always easy and on occasion it was evident that dead skin had been sutured.

The second cause of skin trouble was from the incision leading to death of some part of the skin flap. This varied from a little moisture at the edge to the death of the whole flap. The severe degrees were uncommon and associated in almost all instances with serious infections where the viability of skin was in doubt. In some cases a right-angle incision was used instead of a curve and led to an area of necrosis at the corner. One complication which was associated with these difficulties was haematoma formation. It was infrequent and usually associated with some break in the technique such as changed site or shape of incision or variation of routine in relation to the tourniquet.

Complete excision of non-viable tissue is an absolute essential to uniformly good results and is the aspect of the procedure which requires most thought and care. There were a number

of instances in which the operator was satisfied that he had carried out an adequate excision and his error was due to the absence of localisation. There were others in which suture was mistakenly carried out after what was known to be inadequate excision.

These are briefly the reasons for the failures and it is difficult to generalise about the relative frequency and importance of the various causes. For example, of the 226 distal pulp space infections there were ninety-three which failed to heal per primam, and in the detailed analysis of these it was found that in more than half the delay in healing was due to the granulation of a sinus or a small part of the incision—in none of these was there retained infection or significant symptoms after the operation. In only thirteen was inadequate excision apparently the cause of the delay.

DISCUSSION

Our main purpose is to report results and no attempt is to be made to discuss all aspects of the problem or to comment on recent papers. It is proposed to mention only those items which seem to be of importance to this report.

One is the conflict of opinion on the relative importance of ischaemia from tension and the effect of the staphylococcus on the tissues. It seems likely that these factors are complementary in producing the sequence of events which leads to extensive tissue destruction. The only way the tissues have of resisting the proteolytic effect of the organisms is to increase the concentration of antibodies by increased blood flow. When the infection is controlled at the stage when some tissue has been destroyed and a localised abscess formed, the problem is still a relatively simple one. There is, unfortunately, a high proportion in which the resistance is inadequate and the process does not stop until extensive tissue destruction has taken place.

The cellulitis around the site of primary infection varies considerably and is sometimes a useful guide to the prognosis. An active reaction might well be expected to signify an early localisation. This sometimes follows, but more often it is an indication of the inability of the tissues to contain the infection and at this stage surgery should be delayed until it has been possible to see the effect of penicillin. The absence of a brisk cellulitis may engender a false sense of security, as there may be little or no reaction around an infection which is quietly and progressively destroying the whole of a pulp space.

In any particular case in which both factors—staphylococcal toxin and local tension—are operating, it is essential that both should be dealt with as quickly as possible. Once pus forms in any of the spaces in the hand there is no evidence to suggest that it resolves in any significant number of cases; it is therefore essential that it should be removed.

In distal pulp infections the diagnosis and treatment of osteitis is a problem which receives much attention. Bone infection was present in a very small proportion in this series. This is probably due in part to the stage at which they were seen and to the treatment given, but even more to the fact that osteitis was based on a clinical rather than radiological diagnosis. In any severe pulp space infection radiographs will at some stage show changes in the phalanx which may be diagnosed as osteitis. The most common change is a diffuse osteoporosis from persistent hyperaemia, similar to the changes seen in the bones around the knee joint in a chronic synovial infection. If the hyperaemia and/or the treatment is sufficient to deal with the infection no further changes occur. If it is not, then the bone may become infected. It is sometimes surprising to see extensive bone changes shown in the radiograph return to normal without any sequestration.

The difference of opinion with regard to the value of antibiotics in the treatment of hand infections raises points of interest and importance. Culture of the organisms was done in a large proportion of the cases and the results were similar to those in most other series. It is interesting to note that of eighty-two staphylococcus aureus infections in which penicillin resistance was tested not one resistant strain was found.

Little is said about the value or otherwise of poulticing, the form of early treatment accepted by all laymen and many general practitioners. It probably does a good deal of harm in certain types and stages of infection.

In the early stages, before pus is present, every infection has been given the opportunity and assistance to subside and this has been done with immobilisation and adequate penicillin for five days or more. Even when pus was present, with a good deal of cellulitis around the site, a period of up to twenty-four hours' immobilisation and penicillin was found to be of value before surgical intervention.

One great difficulty in the early stage is to be certain whether or not pus is present. This problem is one with which we would like to be confronted more frequently—in all too many of the fingers there is no room for doubt. That it is not frequent enough is borne out by the fact that in only 4 per cent of the patients operated on was no pus found.

Technique—A brief review of some aspects of the technique used is perhaps justified. *The anaesthetic*—We are more firmly of the opinion that general anaesthesia is the method of choice for any deep finger or hand infection and that ring block for fingers should be condemned. More remote regional anaesthesia has a place under certain conditions. *The incision*—The incisions described in the previous paper were worked out with great care and when they have been adhered to there has been little trouble. For various reasons it is not always possible to adhere to them and in the attempt to excise the lesion adequately incisions have been turned and extended, with consequent trouble with flaps in some cases and delayed healing. This is of sufficient importance to suggest that the procedure should be abandoned when modification of incision becomes necessary. *The excision*—The technical difficulties of excision have already been mentioned. It is difficult to get people to distinguish between " dead " and " infected " tissues—not surprising perhaps when we remember that this difficulty led to so much of the disagreement about wound excision during the war. *Suture*—The three essentials here are adequate excision, viable skin flaps and no damage to main blood vessels. When there is any doubt about the efficiency of the excision the wound should be left open and skin of doubtful viability should not be sutured. When there is no retained infection sutures should always be left in for ten days, and longer if desired, even after mobilisation is started. *Immobilisation* must be effective to be of any value, but on no account must it be tight.

In the series of cases analysed above there has been no attempt to make a comparison of the results with any parallel series treated by other methods. The series comprised about two-thirds of all septic hands operated on in the period under review; the remaining cases were for the most part minor ones in which excision and suture were clearly unnecessary. It will be noticed that the incidence of paronychia is lower and the incidence of tendon sheath and palmar space infections much higher than in most recently published series.

There is no simple or single answer to the treatment of hand infections. In theory there is no doubt that excision and suture is the ideal method and we must therfore try carefully to determine those cases most suited to this method. In practice we were aware that difficulties existed and this review has made it possible to assess them.

INDICATIONS AND CONTRA-INDICATIONS FOR EXCISION AND SUTURE

This method is designed to give the patient the best possible treatment when adequate facilities are available. It is in the more severe and serious infections that it finds its greatest application, and as a matter of principle the treatment of severe hand infections ought not to be undertaken without adequate facilities for careful and unhurried surgery. It is not a suitable technique for use in general practice.

Its chief advantages are the way in which severe infections can be controlled by it, the lack of post-operative pain and the fact that frequent dressings are not required. This saves

the patient much time and discomfort, and incidentally cuts down work in the casualty department and reduces the amount of dressing materials used.

It should be used when there is a well localised infection—where pus can be removed, all dead tissues excised and healthy skin sutured without tension. In tendon sheath infections its use is clearly indicated, for these give unsatisfactory results when dealt with by simple drainage methods. It can deal with the ramifications of multilocular abscesses, such as are found in the palm and distal palmar spaces, more effectively than any other method. It is a good way of eradicating small, deep-seated abscesses such as are found in the distal pulp space.

It should be avoided when the infection is poorly localised and the dividing line between dead and living tissue poorly demarcated, and when the infection is so extensive that complete excision is not practical. Those cases in which there is a sinus that cannot conveniently be included in an orthodox incision or in which the viability of the skin about the sinus is in doubt are better treated by some form of simple "unroofing" procedure. This is because, by the time a sinus has formed, multilocular abscesses have usually coalesced into a single collection of pus which is easily drained. Nevertheless excision, with or without suture, can often play a useful part in the late treatment of distal pulp infections with sequestra and sinuses. In superficial infections—including apical, dorsal and palmar—simple drainage will lead to equally rapid healing.

Apart from its therapeutic value, the exposure provided by this technique has taught us a good deal about the detailed pathology of the infected finger. It has shown us that diffuse cellulitis is not limited to streptococcal infections, and has demonstrated how an infection tracks from one pulp space to another and thence to the palm along the neurovascular bundles, and how it spreads along the fibres of the palmar fascia in distal web space infections to involve one space after another. We have seen how often the clinical diagnosis of tendon sheath infection is wrong, and also how often an unsuspected sheath infection may be present.

SUMMARY

1. A series of 1,211 cases of infection of the hand and fingers is reviewed. Of the 1,066 which required operation about two-thirds were treated by excision and suture, and the results in these cases are analysed.

2. The criterion of success was per primam healing in seventeen days or less, and 54 per cent of the cases treated by this method (excluding paronychiae) fulfilled this criterion.

3. The causes of failure are discussed.

4. It is concluded that excision and suture is the method of choice in well localised infections, but that it should be avoided in diffuse infections and in some cases with sinuses. Its use is unnecessary in trivial infections.

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RETICULUM-CELL SARCOMA OF BONE*

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Over a quarter of a century has elapsed since Ewing (1921) described the "diffuse endothelioma of bone," a specific clinical entity of a characteristic pathological appearance, but wide differences of opinion still exist concerning the pathological histology of the tumour and only mere hypothesis about its histogenesis. This is so despite the fact that numerous papers have been published on the subject (Kolodny 1927, Connor 1926, Coley 1949, Geschickter and Copeland 1949, Geschickter and Maseritz 1939, Meyerding and Pollock 1940, Meyerding and Valls 1941, Campbell and Hamilton 1941, Stout 1943, Lichtenstein and Jaffe 1947, and Brachetto-Brian 1946).

Connor (1926), after a survey of the fifty-four cases then in the American Registry of Bone Tumours, distinguished three histological types: 1) the angio-endothelioma; 2) the diffuse endothelioma; and 3) the reticular type of tumour, which probably originates in the reticulo-endothelial elements of the bone marrow. Thus begins a histological subdivision of Ewing's tumour, enlarged later in the fundamental papers of Oberling (1928) and Oberling and Raileanu (1932). These authors endeavoured to show the analogy between Ewing's tumour and the reticulo-sarcoma of lymph nodes, believing in the pluri-potentiality of the reticulo-endothelial cell (for instance, its possible reticular, endothelial, myeloid and lymphoid differentiation); they suggested the term "reticulo-sarcoma of the bone marrow" for these growths. They divided them into various groups (undifferentiated reticulo-sarcoma, reticulo-endothelial sarcoma, differentiated reticulo-sarcoma, reticulo-myelo-sarcoma, and reticulo-lymphoid sarcoma) but, like Connor, they made no distinction between the clinical evolution of the different types.

Parker and Jackson (1939), after a new survey of the American Registry of Bone Tumours, drew attention to a malignant bone tumour which they termed "primary reticulum-cell sarcoma of bone." They endeavoured to separate it from Ewing's sarcoma, with which it had been previously identified. They were able to collect seventeen examples of this new type from their own cases and those of the Register (this number increased to twenty-five in 1947). Parker and Jackson noted, as a characteristic clinical feature, the discrepancy that often exists between the size of the destructive bony lesion and the good general condition of the patient; they also pointed out that the clinical evolution seems more favourable than in Ewing's tumour, seven out of seventeen patients having survived over ten years. Histologically the basic tumour-cell is identical with that of the reticulum-cell sarcoma of the lymphatic glands and other tissues; moreover, numerous reticulin fibres are seen separating, not only cell groups, but also individual cells, contrary to the appearance in Ewing's sarcoma.

It seems clear that Ewing accepted Parker and Jackson's opinion when, in his revision of the American Register Classification (1939) he included the reticulum-cell lymphosarcoma as a new entity, thus differentiating it from Ewing's sarcoma. Both in the latest edition of his book (1940) and in 1942 (personal communication to Stout) he maintained this distinction; in discussing Oberling's (1928) hypothesis he commented that the mother-cell of the tumour bearing his name cannot form reticulum cells or blood elements (red or white). He further stated that if this took place, the growth would be a reticulo-lymphosarcoma or a myeloma,

* Paper read by Professor José Valls at the Nuffield Orthopaedic Centre, Oxford, on April 26, 1951.

but not a Ewing sarcoma. More recently other authors (Simmons 1939, Edwards 1940, Szutu and Hsieh 1942, Gall and Mallory 1942) have reported further cases and, together with that of Edwards describing a necropsy, they all seem to confirm the existence of a primary reticulum-cell sarcoma of bone.

Stout (1943), on the contrary, is unable to separate Ewing's sarcoma and the reticulum-sarcoma into two distinct groups. He states that, in his opinion, the cell structure of both groups is so interwoven that, "with Oberling, he must admit that they are nothing but mere variants of the same tumour." Nevertheless, Stout, like Lichtenstein and Jaffe (1947) later on, does not accept the pluri-potentiality of the basic cell of Ewing's sarcoma, because he claims never to have observed any vascular or haemopoietic differentiation of the cells. These authors, notwithstanding, are more inclined towards Oberling's hypothesis—which claims that the basic cell derives from the reticulo-endothelium cells and undifferentiated mesenchymatous cells of the marrow—than to that of Ewing, who believed that the cell originates in the endothelium of the blood vessels.

Lately Sherman and Snyder (1947), after a radiological study of seventeen cases, concluded that the diagnosis can be reached, or at least suspected, by the radiological appearance alone. This opinion is shared by Coley who, by 1949, had been able to collect twenty-three cases. It should be emphasised that there is an overlapping of several cases of American writers, as some taken from the Registry of Bone Tumours had already been included in the works of Parker and Jackson (1939, 1947).

From this review, it is clear that there is need for an exact histological and histogenic interpretation of this group of tumours, and especially for a definite histological segregation of Ewing's sarcoma from the primary reticulum-cell sarcoma of bone. This need becomes more obvious if we are able to confirm that the latter has a more favourable clinical evolution.

CLINICAL MATERIAL

During the last eight years we have been able to study, from clinical, radiological and pathological aspects, ten cases of primary reticulum-cell sarcoma of bone and thirty-five of Ewing's sarcoma. This survey includes only seven cases of reticulum-cell sarcoma (Table I) and twenty-five of Ewing's sarcoma, because we have omitted those of recent observation and those about which full data are not yet available. In five cases of reticulo-sarcoma we studied the specimens obtained from surgical excision or amputation and a detailed post-mortem examination was carried out in four cases of Ewing's sarcoma. In most of the microscopic studies, in addition to the orthodox histological methods, Hortega's techniques of silver impregnation were employed, particularly those recommended for reticulo-endothelial elements and reticulin fibres. These techniques have been invaluable in the histo-pathogenic interpretation and histological subdivision of both tumours. When it has not been possible to use these techniques, the staining has always been carried out according to those recommended by Foote and Gomori. The results of these histological investigations have been published recently in detail by Polak and Schajowicz (1949), and in the section devoted to pathology we shall refer to the conclusions reached by these authors.

CHARACTERISTICS OF RETICULUM-CELL SARCOMA

The following are the principal pathological, clinical and radiological features we have found in primary reticulum-cell sarcoma of bone.

Pathology—In the four cases in which we were able to study the anatomical specimen the tumour had destroyed the cancellous bone over a wide area, and the cortical bone was distended and perforated at several points. The periosteum had never reacted or produced new bone, although this did occur on a small scale in the cancellous tissue surrounding the tumour. The consistency of the tumour varied between firm and friable. Histological studies were rendered easier by invariable absence of the necrotic areas seen in Ewing's sarcoma.

In one of our cases there was a bone and lung metastasis, and in another, in which the tumour occupied the femoral diaphysis, the inguinal glands were invaded. In two other cases, in the patella and tibia respectively, the inguinal glands were examined but no deposits were found. We have discarded one of our cases which showed simultaneously invasion of the inguinal glands and bony lesions of the pelvis, as it was difficult to be certain whether we were dealing with a primary or secondary reticulum-cell sarcoma of bone. The same doubt was present in the cases of Edwards (1940), Szutu and Hsieh (1942) and Khanolkar (1948), which showed similar invasion of the regional glands.

Histological structure—With the ordinary staining techniques the tumour is characterised by an intense proliferation of its cellular elements, the slightly basophilic cytoplasm of which is

TABLE I

SUMMARY OF THE MOST IMPORTANT FEATURES OF SEVEN CASES OF RETICULUM-CELL SARCOMA

	Age (*years*)	Evolution	First symptom	Site	General condition	Treatment	Recurrence	Metastasis	Later results
Case 1	8	10 months	Tumour	Radius	Normal	Radiotherapy	3 years	Lung—nine years after onset of symptoms	Died ten years after onset
Case 2	25	10 months	Tumour and pain	Tibia	Normal	Excision, graft and subsequent amputation	2 years	None	Well nine years later
Case 3	42	2 years	Pain	Pelvis	Affected	Radiotherapy	None	None nine years after onset of symptoms	Died ten years after onset
Case 4	45	1 year	Pain	Patella	Slightly affected	Excision	None	None	Well five years later
Case 5	38	10 months	Pain	Pelvis	Normal	Radiotherapy	None	None	Died three years later from pneumonia
Case 6	71	1 month	Pain	Sacrum	Severely affected	Curettage and graft	1 year	Lung	Died one year later
Case 7	25	2 years	Pain	Tibia	Normal	Excision	None	None	Well two years later

often seen clearly outlined, although sometimes presenting a diffuse appearance with ill-defined cell margins (Figs. 1 and 2). The large nuclei, usually poor in chromatin, vary in shape between oval, lobulated and reniform; occasionally more than one nucleus can be seen. Generally there are one or more large well-stained hypertrophic nucleoli. Sometimes the impression is gained that these cells show a marked haemopoietic—especially lymphocytic—evolution. Blood vessels are intimately associated with the tumour elements, which on many occasions are seen invading the wall of a large vessel. Hortega's specific technique shows the wealth of the reticulo-endothelial elements in this type of tumour and their even distribution among the more differentiated cells. Their shape is variable, predominantly ramified, although sometimes ameboid or rounded, and their association with the walls of the blood vessels is evident (Figs. 3 to 6).

The distribution of the reticulin fibrillar network is a fundamental feature. Starting at the adventitia of the blood vessels as a close mesh, it gradually becomes more open, though always maintaining the retiform tendency of forming small or medium-sized areolae containing isolated or small groups of tumour cells (Figs. 3 and 4).

In contrast, Ewing's sarcoma, by orthodox staining methods, reveals a compact mass of cells of uniform shape, with rounded or oval nuclei, indistinct nucleoli, and usually ill-defined and scanty cytoplasm. In such tumours Hortega's techniques show the reticulin fibres circumscribing large areas containing many cells, forming lobules into which no fibrillae (or very few) penetrate (Figs. 7 to 10). Moreover, the morphologically different reticulo histiocytic elements are very rare among the tumour elements and somewhat more numerous among reticular and collagen fibrillae surrounding the lobules. It should be stressed that we have never observed any differentiation whatsoever of the fundamental cell of the tumour, except a vascular adaption that could be interpreted as an angio-endothelial differentiation of the tumour cells (Polak and Schajowicz 1949). The clear difference that these two authors draw

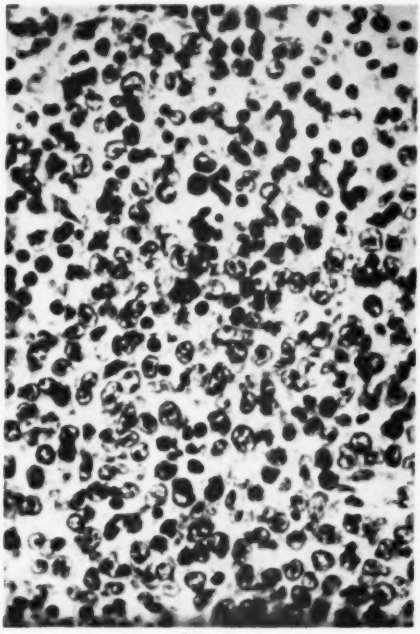


FIG. 1

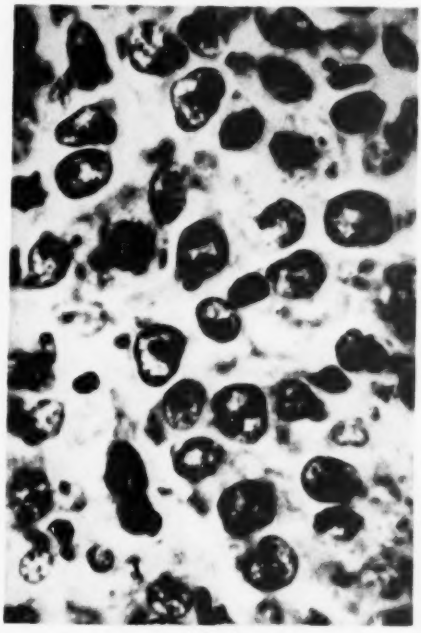


FIG. 2

Reticulo-sarcoma seen at low and high magnifications (from Case 2). They show the typical cytology of the tumour and the differentiation of the reticulo-histiocytic mother-cell. (Haematoxylin-eosin.)

between the two types of tumour is in contrast with other investigators, to some of whom this distinction is not yet acceptable (Stout 1943, Lichtenstein and Jaffe 1947).

Clinical picture—Our statistics are based on the study of seven cases (Table I). In general the clinical and radiographic features of our observations coincide with those described by Parker and Jackson (1939). Three cases of femoral, tibial and iliac tumours have not been included because the clinical and radiological data are not yet complete.

Of the seven patients five were male and two female. Their ages were eight, twenty-five, twenty-five, thirty-eight, forty-two, forty-five and seventy-one years. The sites of the tumours were tibia (two cases), pelvis (two cases), sacrum, radius and patella. The patellar site (Fig. 18) is singular, and we have not found it previously mentioned.

These tumours typically do not affect the general condition of the patient; a deterioration was appreciable in only one of our patients, aged seventy-one, except that two others lost weight slightly.

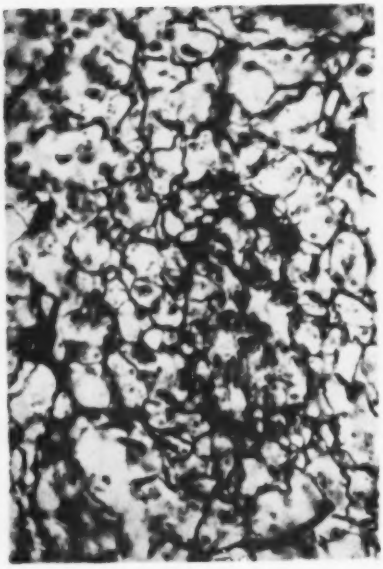
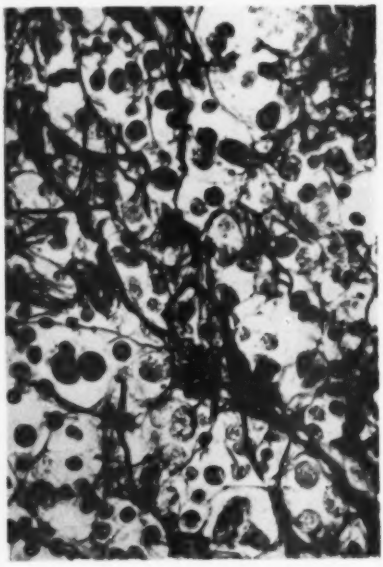


FIG. 3



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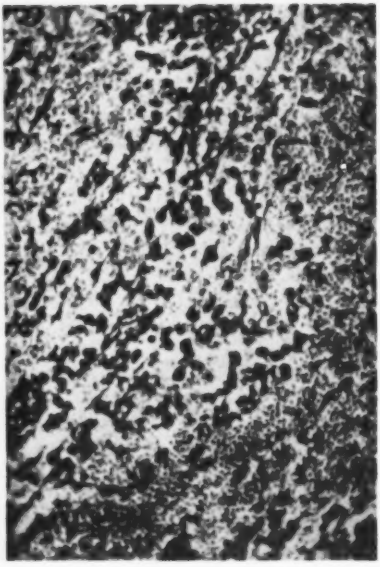
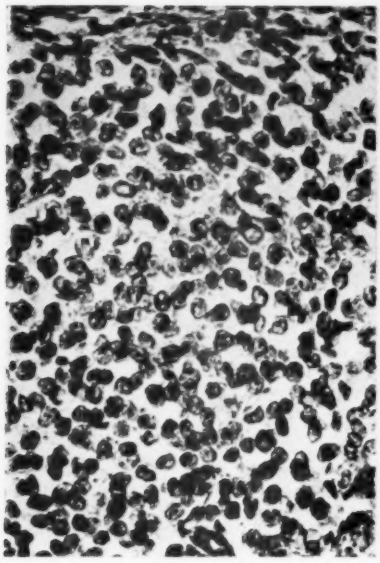


FIG. 5

FIG. 6

Reticulo-sarcoma stained with Hortega's techniques of silver impregnation. In Figures 3 and 4 reticulin fibres can be seen adopting the form of a thick close-mesh network which surrounds individual or small groups of cells. Figures 5 and 6 show the staining of the reticulo-endothelial elements; a large number of these are seen to be affected by the neoplasm.



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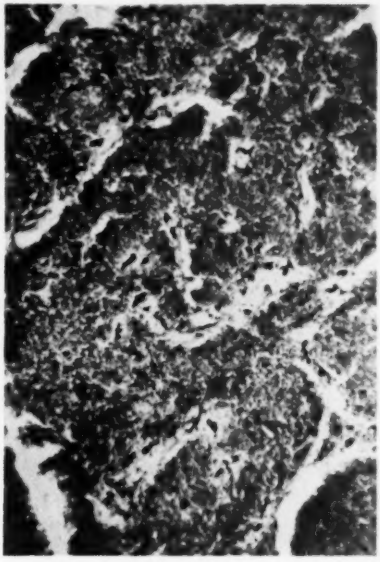

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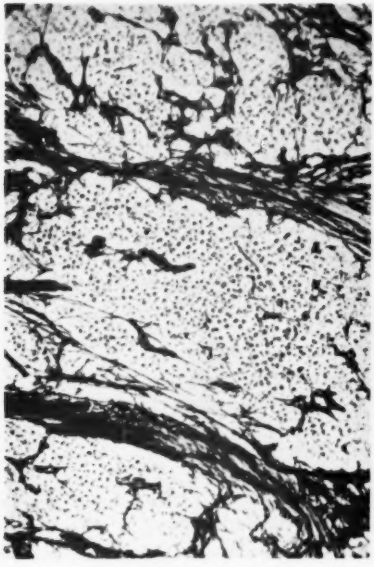

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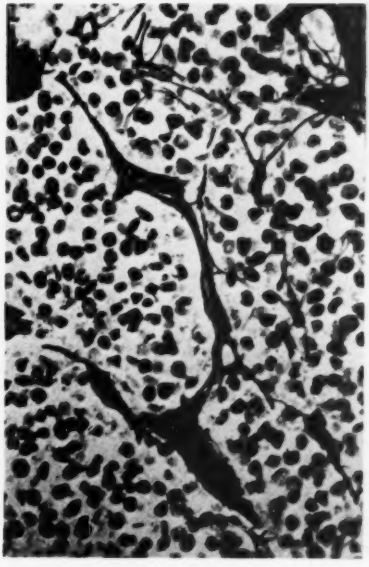

FIG. 10

A case of Ewing's sarcoma with its cell elements of uniform appearance. Figure 7—Scanty reticulo-histiocytic elements situated in the septae separating the tumour lobules. Figures 8, 9 and 10 show the lobular distribution of the reticulin network which surrounds large cell areas (Hortega's techniques).

The onset is insidious and the evolution slow. Six of our patients consulted us between ten and twenty-four months after symptoms began. Pain is the initial symptom, yet it never

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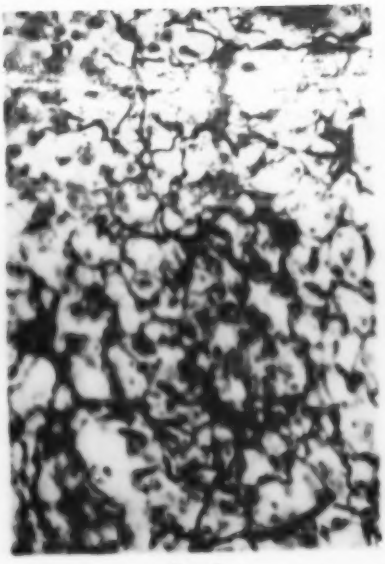

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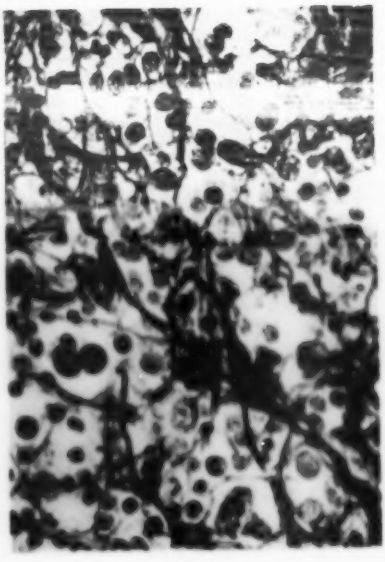

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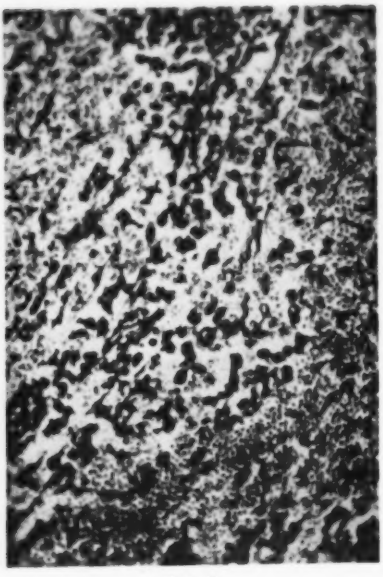

FIG. 5

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The onset is insidious and the evolution slow. Six of our patients consulted us between ten and twenty-four months after symptoms began. Pain is the initial symptom, yet it never

FIG. 11

FIG. 12

FIG. 13

FIG. 14

FIG. 15

Case 1—Reticulo-sarcoma of radius. Figure 11—Initial radiograph. Figure 12—One year later. Figure 13—One year later still, after radiotherapy; the appearance of the bone is almost normal. Figure 14—Recurrence one year later. Figure 15—Three years later, after further radiotherapy. Death from metastasis ten years after onset.

attains the intensity found in some other malignant growths. In only one case was the local swelling the first feature to attract the patient's attention. Pathological fracture was observed in two cases. In one the tumour was in the patella, which snapped during a strong contraction

FIG. 16

FIG. 17

Case 2—Reticulo-sarcoma of tibia. Figure 16—Early radiograph. The tumour spread later to the metaphysis and epiphysis (Fig. 17). Excision was carried out after radiotherapy. Two years later there was a recurrence which called for amputation. At present, six years after this operation, the patient appears to be well.

of the quadriceps muscle. In the other the tumour had destroyed a large part of the acetabulum, and this broke under the weight of the body.

Radiographic findings—The tumour is essentially osteolytic. In the long bones it arises in the marrow of the metaphysis or epiphysis. It spreads rapidly towards the cortex, which it destroys, and then invades the soft tissues (Figs. 11 to 18). The absence of reaction on the part of the cortex and the periosteum is a valuable aid in differential diagnosis. There is a total absence of the spicular images apparent in Ewing's sarcoma and some of the osteogenic sarcomas (Figs. 19 to 21). In one of our cases (Case 1, Figs. 11 and 12) the radiographs showed the tumour distending and thinning the cortex, but not perforating it; the appearance was that of a "blown up" bone. In the remaining cases, destruction took place without gross changes in the architecture of the bone (Figs. 16 to 18).

The radiographic appearance of total lysis is not always found. Sometimes bony trabeculae remain within the area of destruction and produce a multilocular appearance (Fig. 17), as is typically seen in the giant-cell tumours and in hydatic disease. The progress of the tumour as observed in serial radiographs is rapid, and the osteolytic process ends by affecting a large area of the bone in which it began. The disproportion between

FIG. 18

Case 4—Reticulo-sarcoma of the patella. Radiograph shows appearance after pathological fracture. The osteolytic appearance of the process can be clearly seen. The patient is well five years after excision of the tumour.

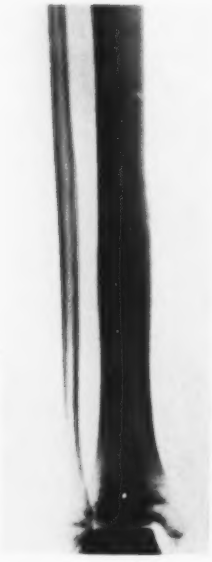

FIG. 19

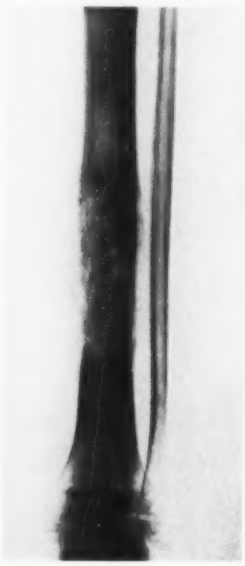

FIG. 20

FIG. 21

Radiographic evolution of Ewing's sarcoma. The lesion began as a sclerosed lesion (Fig. 19). Later there were areas of osteolysis and periosteal reaction in the shape of "onion peel" (Fig. 20). Radiating spicules appeared after radiotherapy (Fig. 21).

the patient's good general condition and the radiographic extent of the lesion is typical of these tumours.

DIFFERENTIAL DIAGNOSIS OF RETICULUM-CELL SARCOMA

The differential diagnosis must be made from the osteolytic types of osteogenic sarcoma, Ewing's sarcoma, secondary bone metastasis, multiple myeloma and hydatid disease.

TABLE II

PRINCIPAL FEATURES OF RETICULUM-CELL SARCOMA AND EWING'S SARCOMA

	Primary reticulum-cell sarcoma	Ewing's sarcoma
Age (*years*)	Between 20 and 50	Between 8 and 16
Site	Either in epiphysis or metaphysis of long bones	In metaphysis and diaphysis
Radiograph	Osteolytic lesion without either reactive or tumour osteogenesis	Initial bone condensation; later osteolytic, and periosteal osteogenesis in the shape of "onion peel"
General condition	Little altered	Seriously affected
Fever	Absent	Often found
Metastasis	Rare and distant. Found in the lungs and rarely in other bones	Frequent and early. Found in lungs and other bones
Evolution	Slow	Rapid
Prognosis	Relatively high proportion of cures	Fatal in all, or nearly all, cases; only one patient has survived for more than three years

Osteogenic sarcoma is found at an earlier age, has a more rapid evolution and the patient's general condition is usually considerably impaired. Radiological differentiation is impossible. *Ewing's sarcoma*—Although it is still a matter of discussion whether the reticulum-cell sarcoma must be separated from Ewing's sarcoma, we strongly believe that there are clinical and radiological differences (Table II). *Metastatic tumours*—The authors believe that the differential diagnosis is possible only by biopsy. *Multiple myeloma* appears late in life. In contradistinction to reticulo-sarcomata the lesions are found in the spine, pelvis, ribs and skull more often than in the long bones. In many cases there are changes in the urine (Bence-Jones proteosuria) and in the blood (hyperproteinaemia with hyperglobulinaemia). *Hydatid disease*—In this disease, as in reticulo-sarcoma, there is a notable disproportion between the patient's good general condition and the size of the lesions. In hydatid disease the lesions appear to be those of a non-reactive "cold" destruction, as in the primitive reticulo-sarcoma; consequently, diagnosis will be made with the aid of biopsy and blood test.

TREATMENT AND RESULTS

It is difficult to determine the best treatment of reticulum-cell sarcoma, because the number of cases available for study is still small. Parker and Jackson (1939) advised early amputation followed by radiotherapy to the regional glands. Coley (1949) believed that the best treatment is radiotherapy, combined with the administration of Coley's toxins.

Our patients were treated as follows: radiotherapy alone, three patients; excision and radiotherapy combined, two patients; excision, radiotherapy and subsequent amputation, one patient; partial excision and radiotherapy, one patient. Of the three treated with radiotherapy alone, one, with the tumour in the ilium, died ten years after the onset of symptoms (Case 3). In another there was a recurrence after three years, and further radiotherapy was given; the patient remained in good condition for six years, after which a lung metastasis appeared, and death occurred ten years after the beginning of the disease (Case 1, Figs. 11 to 15). The third patient remained apparently well until he died three years later from acute pneumonia (Case 5). Excision of the tumour (with or without bone grafting) and post-operative radiotherapy were carried out in two cases. In one (Case 4, Fig. 18) the patella was excised and post-operative radiotherapy given locally. The patient remained well for five years, but we have been unable to trace him since. The other patient treated with excision and radiotherapy (Case 7) appears to be in good health after three years. In a further patient (Case 2, Figs. 16 and 17), excision of the tumour and radiotherapy were carried out, but two years later the tumour recurred and the limb had to be amputated. At present (six years after operation and nine after the onset of symptoms) he is enjoying good health. One patient (Case 6) was subjected to a partial excision of the tumour and radiotherapy, but he died from recurrence ten months after the operation.

Comment—The primary reticulo-sarcoma of bone is very radiosensitive, but radiotherapy does not constitute a guarantee against recurrence, which unfortunately is relatively frequent. In Case 1 a lung metastasis appeared as long as ten years after the onset of the disease. This observation has led us to think that, despite the relatively benign character of these tumours and their marked radiosensitivity, a wide excision of the growth is advisable.

SUMMARY

1. Primary reticulum-cell sarcoma of bone arises from the reticulo-histiocytic elements of bone marrow.

2. The authors have studied ten cases of primary reticulum-cell sarcoma of bone, and have compared the clinical, pathological and radiographic features with those of thirty-five cases of Ewing's sarcoma.

3. In their microscopic studies Hortega's staining techniques were used in addition to orthodox methods.

4. There are histological differences between a reticulum-cell sarcoma and Ewing's sarcoma.
5. Certain clinical and radiographic features help the differentiation between the two tumours.
6. The progress and treatment of the reticulum-cell sarcoma are reviewed in detail.

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SOME OBSERVATIONS ON VENOUS PRESSURE ESTIMATIONS IN THE LOWER LIMB

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In this paper we report an investigation of venous pressures during exercise in ambulant patients. The investigation was undertaken because we wished to assess more accurately the abnormal venous mechanisms in patients complaining of swollen, painful or ulcerated legs. Phlebography, upon which great reliance has formerly been placed, has two limitations. Firstly, it yields only a knowledge of anatomical or architectural venous defects, which may be difficult or impossible to correlate with the accompanying symptoms. Secondly, phlebograms are difficult to interpret and may give misleading information. The method described below has enabled us to obtain functional as well as anatomical data; and from a correlation of the two, a better understanding of many lower leg syndromes has been gained.

With the advent of major surgical procedures for the treatment of post-phlebitic limbs, such as popliteal and femoral vein ligation, it has become more than ever necessary to have reliable objective criteria by which to assess the results of treatment. Rest in bed, healing of the ulcer, adequate bandaging and support, and psychological factors can easily cloud the issue, especially when the follow-up period is a matter of a few months or years. Since an abnormal venous pressure is the most important factor in the causation of symptoms in the post-phlebitic limb, readings taken before and after operation enable the efficacy of the treatment to be judged more accurately.

METHOD

The indirect methods of measuring venous pressure (Beecher *et al.* 1936) are inaccurate in legs with thick indurated skin, and impossible if much oedema is present. Moreover they do not allow the final phlebogram to be performed.

The apparatus that we use (Fig. 1) is a modification of Walker's. A length of polythene tubing with an internal bore of half or one millimetre is introduced through a small incision under local anaesthesia into a superficial dorsal vein of the foot. The vein is tied off distally. Through the tubing is passed normal saline solution from an ordinary transfusion bottle connected with a mercury manometer and bulb. The saline pressure necessary to hold the column of advancing blood stationary in the polythene tubing is taken as the intravenous pressure. If blood does not run immediately into the polythene tube when the transfusing pressure is lowered sufficiently the tube should be gently withdrawn or pushed slightly farther up the vein, as its tip may lie behind a valve cusp. Blood must not be allowed to reach the needle joining the polythene to the rubber transfusing tube because if it does so it may clot; it may even clot within the polythene tube if kept still for too long. It should be remembered that saline is being injected into the patient by a positive air pressure, and precautions must be taken to replenish the saline as necessary.

With the apparatus thus set up, the patient is asked to stand erect and relaxed. After a minute or two, when the pressure has become stable, measurements may be begun. These are made by lowering the pressure in the apparatus until blood appears in the polythene tube, where it is kept stationary or, during exercise, with a small range of oscillation. The manometer reading is then noted. (The actual pressure at the tip of the polythene tube, with the patient and saline bottle both standing on the ground, is slightly different from the manometer reading. It is equivalent to the sum of the pressures of the column of mercury in the manometer and that due to the height of saline in the reservoir, less that of a column of blood from ground level to the tip of the polythene tube.) The apparatus may be modified

by including a water manometer connected via a three-way tap to the polythene tube. By joining the polythene tube directly to the water manometer, the column of saline which the venous pressure will sustain can be directly noted against the patient's body.

Routine measurements—Four routine readings are taken, all with the patient in the erect position, namely: 1) The resting venous pressure (r.v.p.); 2) the venous pressure with the patient "marking time" by taking about forty six-inch-high steps a minute—the exercise venous pressure (e.v.p.); 3) and 4) the pressures as in 1) and 2) with an Esmarch rubber bandage applied from ankle to knee.

Continuous recordings—We have also obtained continuous records of venous pressure variations in the exercising leg. A short length of capillary tube, with a trumpet-shaped end

FIG. 1

The apparatus used for measuring venous pressure in the lower limb.

over which a tight rubber diaphragm is stretched, is coupled directly with the polythene tube entering the vein. On the diaphragm rests a very light coil moving freely over an iron core. By suitable apparatus, the changes in electrical inductance of the moving coil can be made to produce a direct current, which will give a tracing on a Hughes recorder. Thus pressure variations moving the diaphragm and coil can be continuously recorded. The patient stands on a small platform with a contact arranged to mark the tracing while weight is borne on the leg under examination. A time signal is also incorporated. This apparatus has enabled us to observe the time relationships of pressure variations with exercise. Furthermore, the speed with which the pressure falls during exercise and returns to its resting level can be accurately measured.

Phlebograms—After the pressure readings have been completed phlebograms can be obtained via the polythene tube.

Care of the leg—The apparatus is simple to take down; the polythene tube is withdrawn, the ligatures cut out and a haemostatic pressure dressing applied, to be removed in four or five days. With careful aseptic technique the tiny incision heals by first intention. These investigations can be repeated on the same leg, even elderly patients generally raising no objection. The method is quite suitable for out-patients.

VENOUS PRESSURES IN NORMAL LIMBS

For the assessment of the range of normal pressures, we have investigated the lower limb of healthy volunteers, mostly young adults. The symptomless limbs of patients, many of whom had symptoms in the other leg, have served as controls in the middle-aged and elderly. The relationship of pressures between a superficial dorsal vein of the foot and the deep calf veins is not known, but from the limited studies we have made we believe that the two run parallel, for the rich intramuscular and intermuscular network and the numerous communicating veins between the deep collecting and the superficial systems allow rapid equalisation of pressure.

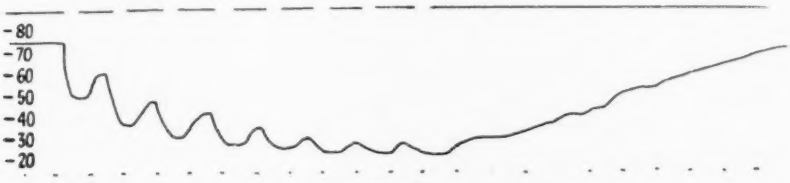

FIG. 2

A continuous record of venous pressure during exercise of a normal lower limb. (The highest trace breaks when the leg under examination leaves the ground. The lowest trace marks the time in seconds. The scale is in millimetres of mercury.)

Standing venous pressure—This approximates to a saline column the height of the manubrium sterni. Mercury manometer readings often showed a slightly lower pressure, but when more precise readings with the fine saline manometer were taken the second intercostal space was usually reached. In the occasional case, however, the standing vertical pressure corresponded to a level below that of the manubrium sterni.

Exercise pressures in the normal leg—The fall of pressure in the superficial dorsal vein immediately exercise is begun is rapid and maintained. It can be studied best by the use of the continuous recording apparatus (Fig. 2). The first tonic thrust of the leg muscles may raise the pressure slightly and a fall does not occur until the foot is lifted from the ground and relaxation of the lower leg muscles has occurred. As can be seen from the tracings the pressure then falls by many millimetres of mercury and if the tonic and relaxation phases are repeated two or three times a plateau level below 60 per cent of the pre-exercise reading is reached. Figure 3 shows the range of percentage falls in exercise venous pressure in a series of patients grouped according to age and sex. Rapid and persistent exercise may cause a further fall and, when measured by the mercury manometer, the readings during exercise may approach zero; continuous and energetic exercise for many minutes in volunteers failed to raise the pressure. The pressures recorded from both lower limbs were alike, never differing by more than 5 millimetres of mercury. The size of polythene tubing or of the dorsal vein did not significantly alter the readings obtained.

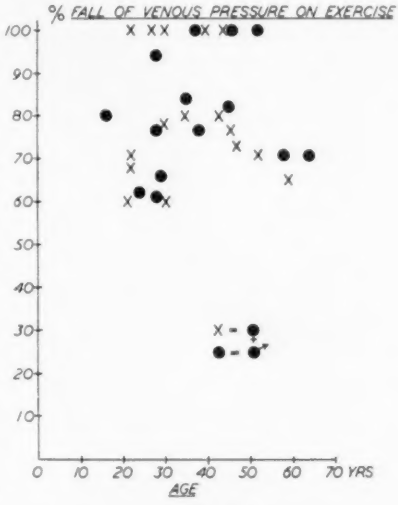

FIG. 3

A graph of percentage falls of venous pressure on exercise of the normal limb plotted against the patient's age.

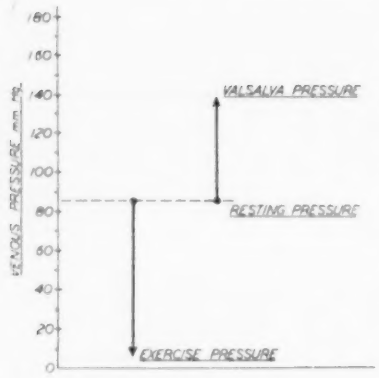

FIG. 4

Diagram illustrating the effects of exercise and a Valsalva test on venous pressure measured in a superficial dorsal vein of the foot in a normal lower limb.

All routine measurements of pressure were repeated after the firm application of an Esmarch rubber bandage from the knee to the ankle. In normal subjects the pressure readings remained within a few millimetres of those before the bandaging. The effect of a Valsalva test (a forced expiratory effort against a closed glottis) on the normal limb is shown in Figure 4. **Some factors in the venous return from the lower limb**—Figures 5 and 6 show phlebograms of a normal leg. The opaque fluid was injected into a superficial dorsal vein of the foot with the volunteer standing erect and relaxed. It will be seen that five minutes later the fluid, whose specific gravity is approximately that of blood, has remained almost stationary. This agrees with the finding of Smirk that the volume of the limb increases perceptibly on standing; and indeed, if the pressure in the deep veins corresponds with that recorded in the dorsal foot veins, it is difficult to understand how an adequate venous return from the lower leg is maintained during the erect relaxed position. In practice the position of standing relaxed without movement of the calf is most unusual

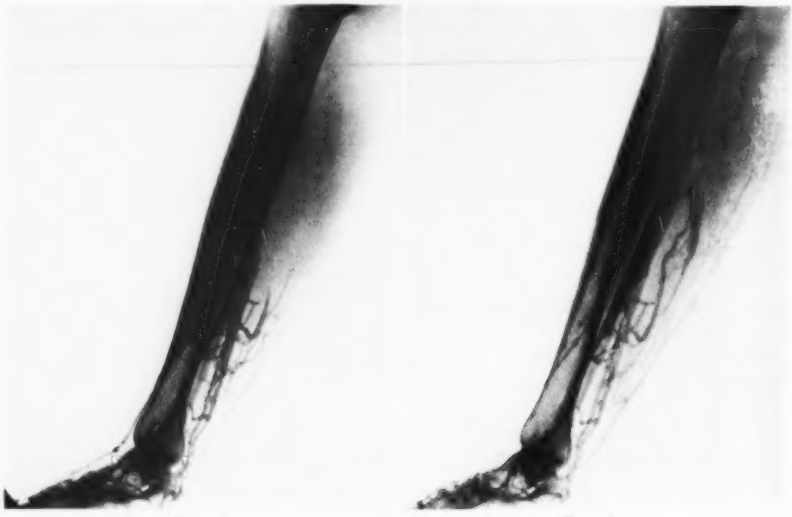

FIG. 5 FIG. 6

Figure 5—Phlebogram of a normal leg immediately after injection of 20 cubic centimetres of 50 per cent diodone into a superficial dorsal vein of the foot. Figure 6—The leg has been kept perfectly still; five minutes later a second phlebogram shows that the diodone has flowed upwards very little.

and needs considerable concentration to maintain it. What normally happens is that the subject moves constantly, now relaxing now contracting the calf muscles. Each small movement causes some return of blood by mechanical compression. When blood reaches the abdomen further factors such as the diaphragmatic pump aid its return.

The anatomy of the lower limb is admirable for the promotion of venous return by exercise. The thick muscles of the calf and anterior compartment are tightly ensheathed in fascia; when the long-bellied muscles contract, their thickest part moves proximally, as is seen readily in the gastrocnemius muscle when the patient stands on tip-toe. This movement massages blood up the deep collecting veins. Furthermore, the rich valvular arrangement in the deep intermuscular veins compels flow in an upward direction. During the relaxation phase the valveless intramuscular veins fill quickly, like a sponge, and the intermuscular veins receive blood from the superficial system as the deep venous pressure falls. The popliteal vein acts mainly as a conduit from the "tibial" to the "femoral" venous pump. High venous pressure may be caused by a defect in either, for instance by tenotomy of the tendo calcaneus, which weakens the calf muscle (Fig. 7), or by ankylosis of the knee, which weakens the quadriceps.

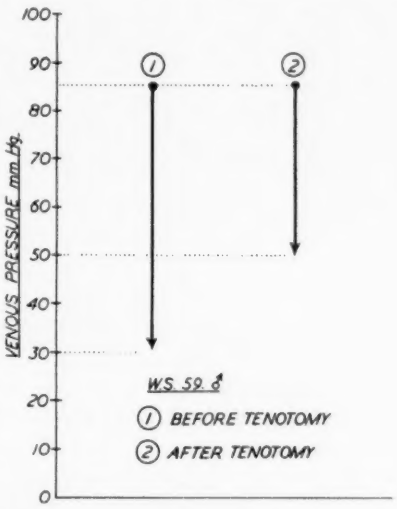

FIG. 7

The effects of tenotomy of the tendo calcaneus on venous pressure measured in the foot.

Pressure readings in other veins—It is difficult to obtain volunteers for venous pressure readings in the major limb veins. Nevertheless standing and exercise pressures were obtained from the common femoral, common iliac and inferior vena cava in three patients. These limited studies suggest that the venous pressure remains virtually stationary at the root of the limb during exercise (Fig. 8). In the inferior vena cava the venous input from the limb exceeds the output, at least during the early period of exercise; consequently the pressure rises, and doubtless aids the venous return to the right side of the heart. The effect of straining and the Valsalva tests are shown on the chart.

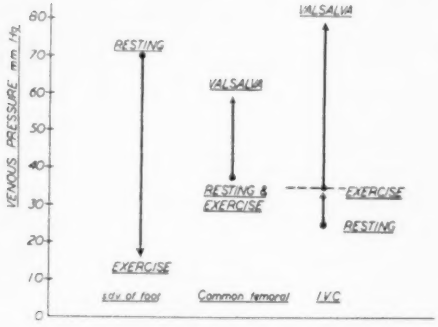

FIG. 8

Diagram to show venous pressure readings, at various levels, on exercise and during the Valsalva tests.

VENOUS PRESSURES IN ABNORMAL LIMBS

The effect of ligation of a major vein—It has long been debated whether a normal major vein should be ligated when the accompanying artery is tied, and the following cases seem relevant.

CASE REPORTS

Case 1—Man aged sixty years. Many years of swelling of the leg with skin changes suggestive of idiopathic elephantiasis. No history of phlebitis. Exercise venous pressures were as follows: standing 90 millimetres Hg.; exercise 30 millimetres Hg. Phlebography showed a normal venous pattern. Ten days after these tests the superficial femoral vein was ligated. Four months later pressure readings were: standing 85 millimetres Hg.; exercise 80 millimetres Hg. The clinical condition was unaffected by the operation.

Case 2—Woman aged twenty-five years. Several years' history of idiopathic lymphoedema. Phlebography showed normal venous system. Ligation of superficial femoral vein was undertaken. Four months later venous pressure readings were: standing 77 millimetres Hg.; exercise 26 millimetres Hg.

Case 3—Woman aged twenty-two years. Orthostatic swelling below knee for two years. No history of phlebitis. Phlebography revealed normal venous anatomy except for previous ligation of what was described by the operator as a normal popliteal vein. Venous pressure six months after operation were: standing 75 millimetres Hg.; exercise 75 millimetres Hg.

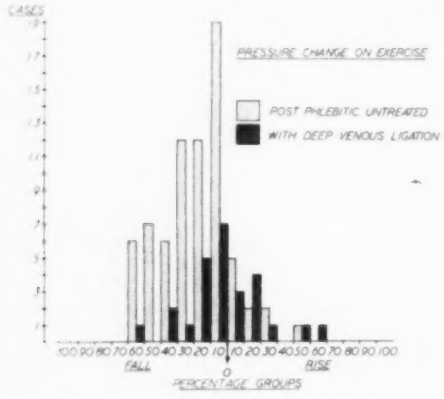
CASES
PRESSURE CHANGE ON EXERCISE
POST PHLEBITIC UNTREATED
WITH DEEP VENOUS LIGATION
100 90 80 70 60 50 40 30 20 10 0 10 20 30 40 50 60 70 80 90 100
FALL
0
RISE
PERCENTAGE GROUPS

FIG. 9

Histogram showing percentage rise or fall of venous pressure on exercise in post-phlebitic limbs untreated, and in those following deep venous ligation. Each column represents the number of cases with percentage pressure changes in the 0–10, 10–20, etc., ranges (percentage groups).

The above case histories indicate that major venous ligation in a limb with normal venous circulation is usually followed by abnormally high venous pressures on exercise. In Case 2 the collateral circulation was adequate to carry the blood flow during exercise, but as years pass the venous circulation will probably become incompetent with consequent pain and swelling.

Venous pressures in chronic deep thrombo-phlebitis—Seventy-two patients have been examined in detail (Fig. 9). The intimate changes in venous pressure readings during muscular contraction and relaxation in the post-phlebitic limb are shown in Figure 10. It is significant that in none did the exercise venous pressure fall below 60 per cent of its resting value and in most it remained high and even rose above the resting venous pressure. The degree of abnormality of venous function depends on many factors, notably the site and extent of the original thrombosis, the development of the collateral circulation and the previous venous pressure readings on exercise.

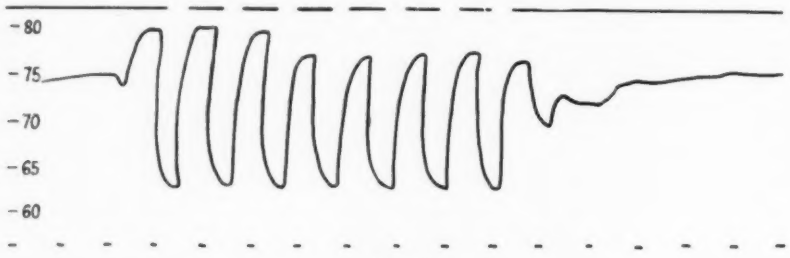

FIG. 10

A continuous venous pressure recording taken during exercise of a post-phlebitic leg.

Although we have never failed to demonstrate reopening of the thrombosed vein, either by phlebography or at operation, its extent seems to have no direct relationship to the degree of inefficiency in the return of blood from the lower limb. As will be discussed later in greater detail, we are of the opinion that recanalisation itself is not the principal factor in the post-phlebitic syndrome.

Abnormal pressure readings are constantly found after acute and chronic deep thrombo-phlebitis, and appear to be the one common etiological factor in the accompanying swelling,

pain and ulceration. We cannot, however, predict the extent or character of the symptoms from a study of venous pressures alone. One patient with abnormally high exercise venous pressure may have virtually no symptoms, whereas another with similar pressure has ulceration, pain and swelling. The application of a firm lower leg bandage has interesting results. In most subjects the standing pressure rises a few millimetres of mercury and the percentage fall on exercise remains as before the bandaging. If there are grossly incompetent superficial varices, the exercise venous pressure may fall considerably.

In a small number of patients, exercise after the application of a bandage causes the pressure to rise, presumably because of the compression of superficial venous " lakes " which act as a buffer or " sluice-mechanism " during muscular contraction. Such patients find a below-knee bandage uncomfortable.

EXERCISE PRESSURE IN PATIENTS WITH VENOUS INCOMPETENCE

In those who have superficial varicose veins, the exercise venous pressure falls less than usual (Fig. 11). A normal fall may be obtained by applying a below-knee bandage or by multiple ligation of the incompetent veins. In some patients without superficial varices or

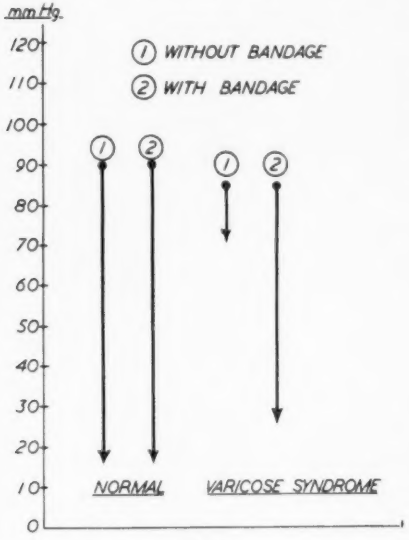

FIG. 11
Typical venous pressure records in legs with normal and varicose veins.

FIG. 12
An ascending phlebogram showing valvular incompetence in the intramuscular conduits.

a history of phlebitis, high exercise pressures are found, and phlebography demonstrates varicosities or incompetence in the collecting or intramuscular conduits (Fig. 12). Such patients with deep venous incompetence may suffer pain, swelling and ulceration. If a history of deep venous thrombosis is obtained and marked superficial varicosities are also present, exercise venous pressure with and without a below-knee bandage enables an accurate assessemnt of the separate lesions to be made.

Traumatic ulcers—This type of ulcer is seen in young people who, after a skin abrasion or laceration, acquire a persistent lesion, usually over the lower tibia. Several have been studied and the following explanation is suggested. If the ulcerated and non-ulcerated legs are examined it is found that the exercise venous pressure fails to fall normally and remains in the 0–60 per cent " fall " range. Some patients have marked deep venous incompetence

although they are as yet free from symptoms. In normal circumstances this is of no importance, but when a skin lesion over the tibia occurs, continued walking and high exercise venous pressure hinder normal skin healing just as in the limb after phlebitis. The continued low-grade sepsis finally gives rise to periostitis. The syndrome of chronic traumatic ulcer is established. Healing is not difficult to secure if the patient is rested and the ulcer grafted before the stage of periostitis is reached, but after this has occurred great difficulty may be encountered.

The effect of a major venous ligation on the exercise venous pressure—The full assessment of major venous ligation (popliteal or femoral) for the treatment of the limb with chronic deep thrombo-phlebitis will be dealt with in detail in a later paper. Twenty-seven cases have been analysed, some with both pre-operative and post-operative venous pressure readings, but in most only post-operative pressures have been obtained (Figs. 13 and 14). Phlebograms give visual proof that the recanalised vein has been adequately tied. Figure 9

FIG. 13

FIG. 14

Figure 13—Phlebogram of post-phlebitic limb before deep venous ligation. Figure 14—The same leg following deep venous ligation of the recanalised channels.

shows that the range of pressure readings is comparable with, or slightly higher than, those in a similar group of patients in whom the operation has not been performed. When pre-operative readings have been done, the major venous ligation has always caused a decided rise in the post-operative venous pressures. Although some patients claimed improvement after a major venous ligation our assessment of the results as judged by amount of swelling and ulceration was disappointing; the beneficial effects sometimes seen may be better attributed to the rest in bed, the healing of the ulceration, the fitting of an elastic stocking, the correction of anaemia and the education of the patient in care of the limb. Indeed we consider that the operation is based on a faulty conception of the important mechanisms involved in the post-phlebitic limb. Immediately after a major vein thrombosis, gross swelling occurs due mainly to the blockage of the main channel of venous return. The collateral venous circulation develops rapidly and within a month or so of the original episode the limb has greatly decreased in size. Exercise pressures at this stage are high. The peripheral venous

circulation can sustain for a time such abnormal pressures, and symptoms are minimal. As the years pass the collateral circulation becomes grossly incompetent, the peripheral venous valves give way and the tissues react to the high venous pressures by producing swelling, pain and other symptoms. The major venous thrombosis occurs within a few months of the incident and varies considerably in degree. The more extensive the original thrombosis the worse are likely to be the patient's symptoms because the collateral venous channels are more tortuous and inefficient. If regurgitation down the recanalised deep vein were of major importance it would be supposed that the longer the segment of recanalisation, the greater hindrance it would be to regurgitation and the less the symptoms. In fact the ligation of a recanalised deep vein by decreasing the venous calibre, through which returning blood can be forced, causes a greater obstacle to the muscular pump and increases the venous pressures and incidence of symptoms. This is in agreement with our clinical venous pressure findings.

CONCLUSIONS

We believe that the technique described is an aid in the analysis of venous abnormalities in limbs. It is simple and safe, and it enables both phlebograms to be made and intravenous pressures to be recorded. Perhaps its greatest use will prove to be in the assessment of therapeutic measures. The protean treatment for leg ulcers illustrates the need for such a criterion.

SUMMARY

1. A technique for measuring venous pressure during exercise is described.
2. The findings in normal and abnormal conditions of the lower limb are recorded.
3. The mechanisms involved in the return of blood from the lower limb in various conditions are discussed, with particular reference to the post-phlebitic state.
4. The need for an objective method of assessing the results of surgical treatment of venous abnormalities in the lower limb is stressed.

We are grateful to the Department of Medical Photography of the Manchester Royal Infirmary for preparation of the illustrations in this paper.

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ACUTE HAEMATOGENOUS OSTEITIS IN CHILDHOOD

A Review of 212 Cases

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This paper is concerned with the observations made on 212 cases of acute haematogenous osteitis admitted to one of the surgical units of the Royal Hospital for Sick Children, Glasgow, during the years 1936 to 1950.

The term osteitis is preferred to osteomyelitis because the bone marrow plays only a small part in bone suppuration (Nowicki 1931, Romanis and Mitchiner 1932, White 1937, and Dennison 1948, 1951). In many centres the older terms periostitis, osteitis and osteomyelitis as denoting separate diseases have been abandoned and the inflammations of bone tissue are alluded to as osteitis, a term which covers all the essential structures of a bone. By "acute" osteitis we mean a sudden illness with severe toxaemia and definite evidence of inflammation of bone, the duration of the illness being days rather than weeks (Williams 1932). Streptococcal osteitis of infancy, by its nature and age incidence, differs from the disease that we are considering (Dennison 1948) and has therefore been excluded from this review.

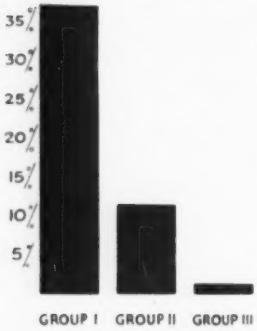

FIG. 1

Mortality in Groups I, II, and III.

The treatment of osteitis falls naturally into three periods: 1) The period before the introduction of chemotherapy. 2) The period of effective chemotherapy. 3) The penicillin "era." The present survey offers an opportunity of assessing the various therapeutic agents in three comparable groups of patients. *Group I* covers the five-year period (1936-1940) immediately before the introduction of effective chemotherapy. The mortality was 36 per cent. *Group II* covers the next five years (1941-1945) when sulphathiazole was used. The mortality fell to 12·7 per cent. *Group III* covers five years (1946–1950) in which penicillin has been used. In this group there has been only one death—a mortality of 1·2 per cent. The mortality in the three groups is shown in Figure 1.

GROUP I: PATIENTS TREATED BEFORE THE INTRODUCTION OF EFFECTIVE CHEMOTHERAPY

Seventy-five patients were treated. Forty-three were boys and thirty-two girls. Their ages varied from nine months to twelve years, but most were over two years (Fig. 2).

Onset—The duration of the disease before admission to hospital is taken from the time of onset of local pain in the limb. This varied from one to ten days, and forty-one patients were admitted within four days of onset (Fig. 5). *Injury and septic focus*—There was a history of injury in forty-one cases (53 per cent) and evidence of a septic focus in twenty-seven (36 per cent). *Bones affected*—The commonest sites were the femur and tibia. The frequency and relative death rate at each site is shown in Table I.

Bacteriology—Blood culture was positive in thirty-eight patients (50 per cent) before treatment began and was seldom positive after the ninth day in those that survived. The

infecting organism (grown from the blood or pus) was staphylococcus aureus in seventy-one cases (95 per cent), streptococcus in three, and pneumococcus in one. Stapyhlococcal infection was responsible for twenty-six of the twenty-seven deaths, the other being due to the pneumococcus.

FIG. 2
Age incidence in Group I.

FIG. 3
Age incidence in Group II.

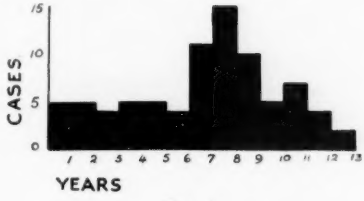

FIG. 4
Age incidence in Group III.

Clinical course—All patients were obviously ill on admission, with a flushed face, bright eyes and dry furred tongue. Examination was usually resented. In many cases the child was comatose on admission and localisation of the lesion was difficult. Even in less severe infections generalised pain and tenderness made accurate diagnosis difficult. The temperature was usually high (103–105 degrees Fahrenheit) but in severe cases a subnormal temperature

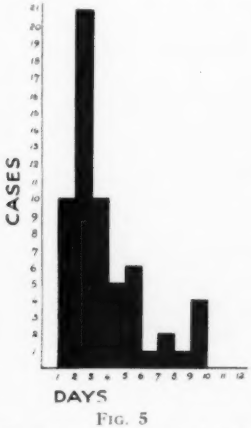

FIG. 5

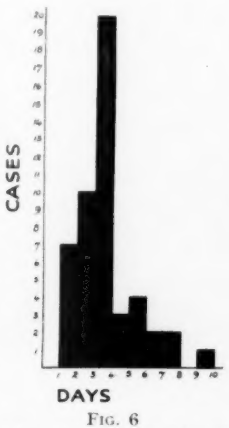

FIG. 6

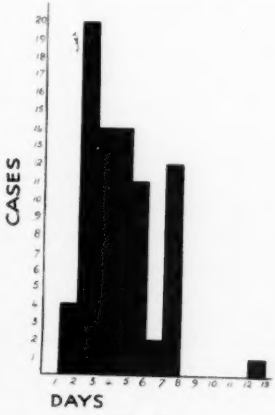

FIG. 7

Figure 5—Duration of pain before admission, Group I (60 of 75 cases). Figure 6—Duration of pain before admission, Group II (49 of 55 cases). Figure 7—Duration of pain before admission, Group III (77 of 82 cases).

was sometimes recorded. Even in the more favourable cases the temperature usually remained elevated for several weeks. In the more superficial bones, local swelling usually appeared early and was followed by erythema of the skin and effusion into an adjacent joint. These

TABLE I

INCIDENCE AND MORTALITY ACCORDING TO SITE OF INFECTION

Bone	Group I		Group II		Group III	
	Number of cases	Deaths	Number of cases	Deaths	Number of cases	Deaths
Femur	22	12	19	1	31	1
Tibia	23	7	18	2	26	—
Fibula	3	1	1	—	—	—
Humerus	7	1	6	—	7	—
Radius	3	—	2	1	1	—
Ulna	3	1	—	—	1	—
Pelvis	2	—	3	1	3	—
Vertebra	—	—	—	—	3	—
Mandible	3	2	—	—	2	—
Maxilla	1	—	3	1	—	—
Ribs	2	1	1	—	2	—
Tarsus	3	—	—	—	2	—
Metatarsus	3	—	—	—	2	—
Scapula	—	—	1	—	1	—
Clavicle	—	—	1	1	—	—
Frontal	—	—	—	—	1	—

classical local signs appeared late in lesions of the pelvis, ribs and upper femur. Leucocytosis was present in all except the most fulminating cases. Rigors usually indicated pyaemic abscess formation, but the presence of such lesions could usually be confirmed only at necropsy. Apart from soft-tissue oedema, radiographic changes were seldom seen before the tenth or twelfth day of the illness.

Duration of stay in hospital of non-fatal cases—Many factors affected the duration of stay in hospital, which is shown in Figure 8. Home conditions often influenced the decision to detain the patient in hospital for a prolonged period.

Radiographic changes—After ten or twelve days a layer of new subperiosteal bone could be seen. Within a few days, areas of rarefaction appeared in the metaphysis, but the changes were soon obscured by dense involucrum formation. The changes almost always extended throughout the shaft, and after four weeks the dense dying shaft could be seen through the more porous involucrum. Over a period of months sequestra of varying size were seen to separate, while the involucrum became even more dense, obscuring the details of bony change.

Mortality—Thirteen of the twenty-seven patients who died succumbed within five days of admission. When death occurred within the first week, there were seldom gross changes in the metaphysis either at operation or at autopsy.

Necropsy findings—Post-mortem examination was carried out in nineteen cases. In all, there were widespread pyaemic lesions. Suppurative pericarditis, abscesses in the lungs and kidneys were common (Table II). In all cases there was a large septic spleen from which abundant staphylococcus aureus was grown.

Complications. *Arthritis*—Of the forty-eight patients who recovered, two presented definite evidence of pyogenic arthritis, without evidence of osteitis in the adjacent metaphysis. Ten patients developed arthritis from direct extension. Two joints were treated by repeated aspiration with return of a full range of movement. Of eight cases treated by open drainage the joint subsequently became ankylosed in four; about half the normal function was regained in three, and only one recovered a full range of movement. *Limb lengthening*—Lengthening of the leg was noted in the case records in seven instances, but no accurate measurements were made in this group and there was no radiographic comparison of the sound and diseased bones. Five of the seven patients were seen again in 1950 and in none was there any measurable

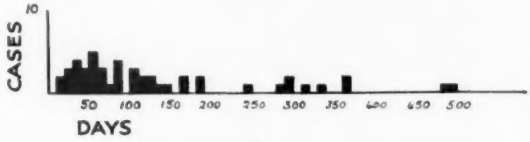

FIG. 8
Duration of stay in hospital, Group I (40 cases).

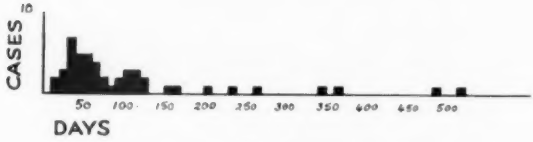

FIG. 9
Duration of stay in hospital, Group II (48 cases).

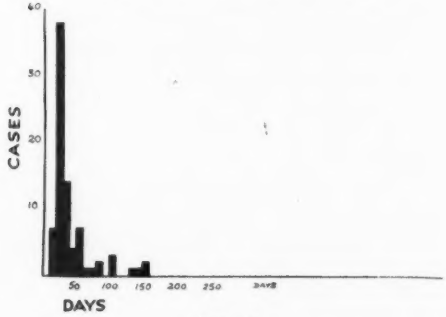

FIG. 10
Duration of stay in hospital, Group III (81 cases).

difference in length of the two legs. *Pathological fractures*—Pathological fracture was common but union occurred with certainty. The support of a dense involucrum usually prevented gross displacement.

Methods of treatment—Treatment during this period was essentially surgical. The use of maggots (Baer 1931) and maggot extract had been abandoned by 1936. The results of administration of intramuscular anti-scarlatinal serum and intravenous mercurochrome were disappointing. Sulphanilamide raised hopes, but even in massive doses it had no effect in staphylococcal infection. Uleron (a dimethyl sulphanilamide) proved useful in the hands of Mitchell (1938) but there was no evidence of any beneficial effect in the cases in this series. Fluid was given freely and intravenous glucose-saline was administered to all acutely ill patients. Exsanguination and replacement transfusion (Robertson 1927) were not used.

The methods of surgical intervention were based on the teaching of Starr (1922) as modified by Winnet Orr (1927). A long incision was made over the affected metaphysis, down to and through periosteum. If much pus was evacuated nothing further was done to the bone, and the wound was lightly packed with vaseline gauze and immobilised in a bivalved plaster-of-Paris case. If no gross pus formation was found under the periosteum, holes were drilled obliquely from the cortex towards the epiphysis, the line of drill-holes extending at least into the centre of the shaft. Although pus was not always obtained, culture of the oedematous marrow or blood oozing from the drill-holes always revealed the infecting organism. Within forty-eight hours pus was usually draining freely. Obvious indications for change of dressing were rise of temperature and increase of local pain.

More radical surgery was sometimes undertaken, and gutters were made in the affected bone in fourteen cases. But it is doubtful whether the more radical intervention gave more

TABLE II

GROUP I: FINDINGS AT NECROPSY IN NINETEEN CASES

Pericarditis	10
Empyema	4
Abscesses in lungs	16
Abscesses in kidneys	15
Arthritis	5
Subcutaneous and intramuscular abscesses	2
Abscesses in heart wall	2
Endocarditis	3
Abscesses in liver	1
Meningitis	1
Suppurative otitis media	1

satisfactory drainage. Primary diaphysectomy (Mitchell 1928) was not performed in any case in this group. White (1935) pointed out that no surgeon who has had to treat a limb in which the shaft has failed to regenerate will lightly embark on primary diaphysectomy (except for the fibula).

Results—In assessing the results of treatment four factors must be considered (Williams 1932): 1) the immediate mortality; 2) the saving of the limb; 3) the extent of necrosis of the bone; and 4) the persistence of suppuration in later years.

The mortality has already been discussed. In no case was amputation necessary. It is almost impossible to assess accurately the morbidity which followed osteitis before the introduction of effective chemotherapy and antibiotics. Sequelae were undoubtedly common, and adherent scars which break down and ulcerate, and discharging sinuses due to underlying cavities and sequestra following osteitis which first occurred during the period under discussion are still seen (Gallie 1951). Only sixteen of the forty-eight survivors were traced. Of these, two still had discharging sinuses with ankylosis of the hip joint. In the others, the wounds were soundly healed, but all the scars were depressed and many were adherent. Four had had further operations since discharge from hospital but radiography revealed no evidence of active bone disease.

GROUP II: PATIENTS TREATED BY SULPHATHIAZOLE

Fifty-five patients were treated. Thirty-one were boys and twenty-four girls. Their ages varied from one to twelve years (Fig. 3).

Onset—The duration of local pain before admission to hospital varied from one to nine days and, as in Group I, most patients were admitted within four days of onset of pain (Fig. 6).

Injury and septic focus—There was a history of injury in twenty-one cases (38 per cent) and a septic focus was found in twenty-two (40 per cent). *Bones affected*—The most common sites were the tibia and femur and the sites and deaths from each are shown in Table I.

Bacteriology—The infecting organisms were staphylococcus aureus (fifty-two cases), streptococcus (two cases), and pneumococcus (one case).

Clinical course—There was no spectacular changes in the course of the disease when treated with sulphathiazole. The duration of fever was shorter and metastases were fewer, but healing

TABLE III

GROUP II: FINDINGS AT NECROPSY IN SIX CASES

Purulent pericarditis	4
Empyema	4
Abscesses in lungs	5
Abscesses in kidneys	4
Arthritis	2
Abscesses in heart	3*
Endocarditis	1
Subcutaneous and intramuscular abscesses	2

* In one case the heart ruptured, causing sudden death on the fourteenth day.

was no more rapid. From a study of the radiographs the degree of bone destruction appeared to be less, but on the whole the changes were very similar to those seen in the previous group. McKeown (1943) reported minimal bone changes in a large proportion of his cases but we could not confirm this. *The duration of stay in hospital* varied from twenty days to just over two years (Fig. 9).

Radiographic changes—The radiographic findings were similar to those in the earlier group.

Mortality—Seven out of the fifty-five patients died (12·7 per cent). Four of the deaths (57 per cent) occurred within fourteen days of admission.

Necropsy findings—Six subjects were submitted to necropsy (Table III). All showed pyaemic lesions similar to those of Group I.

Complications—From the information in the case records it appeared that the complications in this group differ in no respect from those discussed in Group I.

Methods of treatment—In this group surgical intervention was carried out on similar lines to those described for Group I cases. Drilling of the metaphysis and immobilisation in plaster was combined with administration of fluids and sulphathiazole. The dosage of sulphathiazole was based on the minimal effective blood concentration of 2·5 milligrams per cent (McKeown 1943) and was approximately 1 gramme per 20 lb. body weight a day. Sulphathiazole was given for a week; if considered necessary a second course was given three weeks later. In fifteen cases the affected bone was guttered.

Results—The follow-up was disappointing. Only nineteen of the forty-eight survivors were traced. Nine were well with no disability and no radiographic evidence of active bone disease. Of the remaining ten patients, five had been readmitted for removal of sequestra. Four of the ten had marked overgrowth and three moderate overgrowth of the affected limb, and lengthening was measurable in the remaining three patients. Adherent scars were present in four of the ten cases. Two joints (hip and ankle) were ankylosed and one hip joint was subluxated. There was one sinus associated with an intrapelvic abscess. One patient had a flexion deformity of the knee following damage to the posterior aspect of the lower femoral epiphysis.

GROUP III: PATIENTS TREATED WITH PENICILLIN

Eighty-two patients were treated. Forty-eight were boys and thirty-four girls. Their ages varied from one month to twelve years (Fig. 4).

Onset—The duration of local pain before admission to hospital varied from one day to twelve days. In five cases the history of onset was vague; the duration in the other seventy-seven cases is shown in Figure 7. *Injury and septic focus*—There was a history of injury in thirty-seven cases (45 per cent) and evidence of a septic focus was found in twenty-seven (32 per cent). *Bones affected*—The common sites were again the tibia and femur (Table I).

Bacteriology—Blood culture was positive in forty-two cases (51 per cent). The infecting organism was staphylococcus in eighty cases, streptococcus in one, and pneumococcus in one. In two infections (one neonatal) the staphylococcus was resistant to penicillin.

Clinical course—The response of the septicaemia to penicillin, although not immediate, was dramatic. General improvement was usually slowly progressive from the start of treatment but the patient remained ill for several days. Pyrexia continued for a few days, resolving slowly by lysis. The blood culture, if initially positive, was sterile by the third day in all except the two cases in which the organism was insensitive to penicillin. In over 80 per cent of cases pus was present under the periosteum or in the soft tissues on admission, but neither the temperature chart nor the leucocyte count was a reliable criterion for assessing the local condition of the bone. Careful examination of the limb, repeated marrow aspiration and accurate radiographic observation were all necessary when assessing the progress of the bone lesion. With careful immobilisation and relief of tension by surgical intervention when indicated, severe pain was usually abolished in penicillin-treated cases after the second day of treatment. Swelling due to soft tissue oedema usually subsided within seven days. If it remained longer it raised the suspicion of persistent deep pus. *The duration of stay in hospital* varied from twelve days to six months (Fig. 10). Over two-thirds of the patients were home within six weeks.

Radiographic changes—The usual sequence of radiographic changes in penicillin-treated osteitis have been described previously (Dennison 1948). Altemeier and Helmsworth (1945), Higgins *et al.* (1947) and Beerman (1948) reported cases in which the course of disease was typical of acute osteitis but radiographic changes never occurred to confirm the diagnosis. Such cases occur, and we must admit that early treatment may so limit bony changes that they are never sufficiently extensive to be seen by radiography (White and Dennison 1947).

Mortality—Of the eighty-two patients, one died. The organism in this case was a penicillin-resistant stapyhlococcus. Neither streptomycin nor aureomycin was available at that time and, despite massive doses of penicillin and intravenous sulphonamide, the child died on the fourth day. Results reported from other centres are shown in Table IV.

Necropsy findings—There was no pus in the hip joint. A subperiosteal abscess extended for seven centimetres below the greater trochanter. There was no naked eye evidence of a bone focus in the upper femur. There was a large septic spleen and there were pyaemic abscesses in both lungs.

TABLE IV

RESULTS IN ACUTE OSTEITIS TREATED WITH PENICILLIN*

Author	Cases	Deaths	Mortality (*per cent*)
Altemeier and Helmsworth (1945)	34	1	2·9
McAdam (1945)	40	1	2·5
Trueta (1946)	30	—	—
Butler (1946)	14	—	—
Hudson (1946)	37	2	5·4
Higgins *et al.* (1947)	31	—	—
Dennison (1948)	30	—	—
Tucker and Hollenberg (1948)	39	—	—
Wilkinson (1948)	50	—	—
Present series (Group III)	82	1	1·2

* The reports of Higgins, Dennison and Wilkinson deal with infants and children; the others are mixed groups of children and adults.

FIG. 11 FIG. 12

Lengthening of limb after acute osteitis treated by penicillin. In the photograph (Fig. 11) note increased length of left leg and pelvic tilt (correctable by blocks 2 centimetres high). The radiograph (Fig. 12) shows increase in length and girth of left femur.

Complications—Some complications are avoidable, but so long as patients continue to arrive in hospital at a relatively late stage of the disease, complications are inevitable.

Arthritis—Pyogenic arthritis occurred in twelve of the eight-one surviving patients. The joints were involved by direct extension from an adjacent metaphysis. One patient developed scarlet fever on the twenty-fourth day of his illness and was transferred to a fever hospital. There he developed multiple lesions, and he now has a bony ankylosis of the right ankle. In two patients there is gross irregularity of the lower femoral epiphysis. In the other nine cases in which arthritis developed there was recovery of joint movement. One joint was treated by open drainage, with recovery; the other joint infections were treated by aspiration and instillation of penicillin. The infecting organism was a coagulase-positive staphylococcus in all cases of arthritis. The frequent recovery of full joint function was gratifying. Before the introduction of antibiotics, staphylococcal arthritis in children led to ankylosis of the joint in 50 per cent of the cases; the prognosis was much better in streptococcal joint infections (White 1935).

Limb lengthening (Dennison 1952*a*)—In twenty-four infections of long bones treated during 1945 and 1946 measurable increase in length (1–3 centimetres) occurred in thirteen patients (50 per cent) followed up for at least four years. In some, lengthening was not apparent for almost a year after the onset of the acute bone infection (Figs. 11 and 12) and in one patient lengthening of 2 centimetres eighteen months after onset increased to 2·5 centimetres after four years, though there was no clinical or radiographic evidence of active bone disease during this time. Since January 1947 no case of increased length of more than 1 centimetre has been observed. Gross increase in girth and length is uncommon in penicillin-treated cases, but in the earlier cases of this group failure to perform primary suture led to cavitation and sequestrum formation in a number of limbs with resulting overgrowth. When only one of two paired bones is diseased the increase in length affects both bones equally.

Pathological fracture—Despite our awareness of the risks of pathological fracture in the osteoporotic bone in penicillin-treated osteitis (Agerholm and Trueta 1946, Aird 1946, Dennison 1948 *et al.*), this complication occurred on seven occasions. The displacement was usually negligible and there was no pain to indicate the moment of fracture. The fractures have all united, but rather slowly and with little callus formation.

Sequestrum formation—Sequestrum formation necessitating surgical intervention occurred in fourteen cases. The patient who developed scarlet fever on the twenty-fourth day of treatment had metastatic spread of infection from femur to the tibia and fibula of the same limb, and the ankle joint was destroyed by arthritis. Multiple sequestrectomies were required. All the cases in this group were reviewed in 1951 and there was no clinical or radiographic evidence of active bone disease or sequestrum formation in any patient.

Other complications—There was one case of pericarditis, successfully treated by aspiration and instillation of streptokinase. *Hyperaemic subluxation* followed osteitis of the axis. The patient was treated by immobilisation in plaster until the second and third cervical vertebrae fused in the subluxated position. *Adherent scars* developed in only two cases; both scars have been excised with satisfactory results. *Genu valgum* developed in two cases. One patient reported with osteochondritis of the opposite hip fourteen months after recovery from osteitis of the femur. One patient developed a stress fracture of the third metatarsal thirteen months after the onset of osteitis of the femur on the opposite side (Macpherson 1951).

Treatment—The aim of treatment is to control septicaemia and to reduce tension in the local bone focus. If the infecting organism is penicillin-sensitive and penicillin therapy is instituted early, these objects should be achieved without surgical intervention (Florey and Florey 1943). In this group, the average duration of local pain was four and a half days before admission to hospital, and in sixty-eight of the eighty-two cases pus was present under the periosteum or in the soft tissues on admission and surgical intervention was necessary. It is disappointing that cases come to hospital no earlier to-day than they did fifteen years ago.

The details of treatment have been described previously* (Dennison 1948). The frequent intramuscular injections of penicillin cause pain and unhappiness to many of the children and the many methods of prolonging therapeutic action of a single injection (by delayed absorption or by delayed excretion) have been fully investigated. We have found that the blood levels obtained by such methods are too variable to justify our relying on once-daily injections in such a serious infection as acute osteitis. The dose of penicillin suggested in the footnote is often exceeded. Penicillin administration is continued for twenty-one days or until the marrow culture is reported sterile, whichever is the longer period. Should the infecting organism be grown from the metaphysis after twenty-one days, the metaphysis is drilled and penicillin is instilled. Five penicillin-resistant staphylococcal bone infections have been encountered since aureomycin became available (Dennison and Macpherson 1952); the systemic response was dramatic in each case.

Operative procedures—Once an abscess has formed it cannot be sterilised by the systemic administration of penicillin, and in such cases surgery is still necessary. Surgical procedure has been discussed fully in a previous communication (Dennison 1948) and only a brief outline is given here. Despite reports to the contrary (Higgins *et al.* 1947) we have found that aspiration is seldom successful in evacuating the pus. The pus may be too thick to pass through the needle or through the nozzle of the syringe. After aspirating pus as thoroughly as possible, it is instructive to leave the needle in position and to cut down upon the abscess; the quantity of residual pus is usually considerable. In osteitis of the tibia, pus frequently collects between the tibia and fibula rather than on the subcutaneous surface as one might expect; it is difficult to aspirate pus adequately from this interosseous position.

Bone drilling should seldom be necessary, but less harm will be done by bone drilling followed by primary suture of the skin, than by incomplete relief of tension. If pus is present in the soft tissues or under the periosteum, the tension in the bone has probably been relieved. If acute pain persists after simple incision, or if at a later stage one suspects that the blood supply to the bone is inadequate, drill holes without elevating the periosteum will at least give an alternative blood supply and will also allow local instillation of penicillin. Metaphysial decompression (Tucker and Hollenberg 1948) should certainly be carried out if there is any suggestion of tension within the bone.

Guttering and " saucerisation " have no place in the modern treatment of acute osteitis.

* The following is the routine method of investigation and treatment of cases of acute osteitis used at this hospital. 1) Routine history and examination. 2) Blood taken for culture, sedimentation rate. 3) Leucocyte count. 4) Penicillin therapy begun as below (based on dose of 5,000 units/lb. body weight/24 hours).

Age	Dose each 24 hours	Frequency and route
0– 3 months	80,000 units	3-hourly by mouth (aureomycin preferable)
3– 6 months	80,000 units	3-hourly by intramuscular injection
6–12 months	120,000 units	
1– 5 years	200,000 units	3-hourly by intramuscular injection
5–10 years	300,000 units	4-hourly by intramuscular injection
10–12 years	450,000 units	

5) Limb immobilised (but not enclosed) in plaster. 6) *Blood culture* on first, second and third days or until culture is sterile. 7) *Marrow culture* on fourteenth, twenty-first and twenty-eighth days or until sterile. Penicillin level in marrow assayed at same time. Blood calcium, phosphate and phosphatase estimated. 8) Case reviewed daily with special reference to pain, temperature and local condition. 9) Operation only with *penicillin control*. 10) Penicillin continued for twenty-one days or until marrow sterile. 11) *Radiography*—If lesion in doubt, immediate (after giving penicillin); then seventh, tenth, fourteenth, twenty-first and twenty-eighth days; two, three, four and six months and thereafter as required.

Diaphysectomy should never be necessary, but in two cases of extensive osteitis of a rib the necrotic bone was removed and the wound sutured.

Treatment of arthritis—Pyogenic arthritis has been treated by aspiration followed by instillation of penicillin. Aspiration is repeated as required. One joint infection was treated by open drainage. Should the organism prove to be resistant to penicillin, streptomycin should be instilled into the joint after aspiration (Dennison and Macpherson 1952).

Results—Three of the eighty-one survivors have not been traced. Of the remaining seventy-eight, sixty are well and have no disability and no radiographic evidence of active bone disease. Fifteen have measurable increase (from 1 centimetre to 2·5 centimetres) in length of the affected limb, and in two of these there is a postural genu valgum. Of the eleven patients with pyogenic arthritis, one has ankylosis of the ankle and another (in a case of neonatal osteitis) has one and a half inches shortening of the leg four years after gross damage to the lower end of the femur. In the remaining nine patients joint movements are full, free and painless. There are no adherent scars and no sinuses.

DISCUSSION

Etiology—The etiology of acute haematogenous osteitis is not fully understood. The disease varies not only from district to district but also with the resistance of the individual patient, with the virulence of the invading organism and with the massiveness of the dose. *Social incidence*—According to Trueta (1948) the incidence of osteitis is low where the standard of cleanliness is high. In the industrial areas of Scotland there is still appalling overcrowding and in some of the rural districts that this hospital serves, living conditions are poor. It was established that unsatisfactory home conditions existed in fifty-seven (70 per cent) of the eighty-two penicillin-treated cases. Mitchell (1928) stated that there is a definite class distinction in children affected by osteitis, and Stevenson (1946) found that acute osteitis was seldom encountered in private consulting practice. Bailey and Love (1946) state that

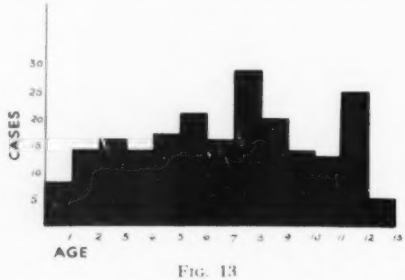

FIG. 13

Age incidence in the whole series of 212 cases.

osteitis is almost unknown in naval schools, although minor injuries and infected abrasions are common. From Salzburg, Domanig (1947) reported that the rural population is more susceptible to osteitis than are the city inhabitants. This is ascribed to poorer living conditions in rural districts.

Age and sex—This hospital admits children up to the age of twelve years, and cases of acute osteitis have occurred in all age groups (Fig. 13). The proportion of boys to girls was approximately four to three (122 boys; 90 girls). These figures are similar to those published by White (1937) from the same hospital and in Table V they are compared with figures from other centres.

Significance of septic foci and injury—The accepted etiology is that a child suffering from a symptomless bacteraemia arising from such septic foci as boils, septic abrasions, infected teeth and tonsils, is subjected to some minor injury to the delicate vascular metaphysis.

There was a definite history of injury to the affected limb within fourteen days of onset of osteitis in ninety-nine of the 212 patients (46 per cent) and evidence of a septic focus in seventy-six (35 per cent) (Table VI). Similar figures are given by Self (1948). Since osteitis never follows a simple fracture, one must postulate that solution in the continuity of a bone allows release of tension in the region of the fracture haematoma.

It is well known that infection can lie latent for long periods in childhood. In the common inguinal adenitis of infancy and childhood the primary focus is frequently healed before the glandular infection becomes apparent. It is hardly surprising that an obvious primary septic focus is found in only about a third of all cases of osteitis; the initial lesion is often healed and forgotten for two or three weeks before the onset of the disease. The daily bumps and

TABLE V

AGE AND SEX INCIDENCE IN ACUTE OSTEITIS

Centre	Author	Number of cases	Age incidence	Ratio of boys to girls
Edinburgh	Fraser (1924) . .	400	8–12 years	6 to 1
	(1926) . .	200	3–10 years	4 to 1
London .	Ogilvie (1928) . .	51	12·9 years (average)	4 to 1
	Pyrah and Pain (1933) .	262	5–14 years	2 to 1
Paris .	Fèvre (1933) . . .	115	4–16 years	2 to 1
Glasgow .	White (1937) . .	200	5–10 years	7 to 5
	Present series (1936–1950)	212	2–12 years	4 to 3

TABLE VI

INCIDENCE OF INJURY AND SEPSIS IN GROUPS I, II, III

	Injury		Septic focus	
	Number	Per cent	Number	Per cent
Group I (1936–1940)	41	53	27	36
Group II (1941–1945)	21	38	22	40
Group III (1946–1950)	37	45	27	32

twists to which the normal child subjects himself may be similarly forgotten. It is unusual to find any local evidence of injury and it is possible that the upset in metabolism which may follow a fright or injury lowers the child's resistance to infection.

Bones affected—The preponderant incidence of infection in the bones of the lower limb (Fraser 1926) is possibly explained by its greater liability to injury.

Treatment—The methods adopted in Groups I and II of the present series are now only of historical interest. With the introduction of penicillin the change in reaction of the patient was so remarkable that the local changes in the bone were neglected or considered inevitable. But it was soon recognised that failure to obtain a satisfactory result was the fault, not of the drug, but of the surgeon. The suitability of a case for penicillin treatment, the details of treatment, and the prognosis depend on exact clinical and bacteriological diagnosis. Four conditions must be fulfilled to ensure a satisfactory result—that is, to control septicaemia,

to prevent the development of metastatic foci, and to induce resolution of the initial bone focus without cavitation or sequestrum formation. 1) Penicillin administration must be begun early (before serious damage to the blood supply with irreversible bone damage has occurred) and the dosage must be adequate. 2) The organism must be sensitive to penicillin. 3) The treatment must be continued until metaphysial culture is sterile. 4) Subperiosteal or soft tissue abscesses must be evacuated and the wound sutured.

After withdrawing blood for culture, forty-eight hours elapse before a report is received on the penicillin-sensitivity of the infecting organism. If a child is acutely ill one must consider the possibility of a penicillin-resistant infection. If the clinical condition of the patient has not improved after twenty-four hours of penicillin therapy (combined if necessary with metaphysial decompression), aureomycin is given and penicillin is stopped (Lankford and Lacy 1949). Nichols and Needham (1949) and Beigelman and Rantz (1950), reporting the increasing frequency of penicillin-resistant staphylococci, state that all their strains have been sensitive to aureomycin.

When assessing the probable effect of penicillin in a particular case the surgeon must not rely too much on the bacteriologist's report. The bacteriologist's medium is very different from the human body and there are at least three problems which the bacteriologist cannot answer: 1) How many organisms is penicillin likely to encounter in the body in any given infection? 2) Do staphylococci produce penicillinase at the same rate *in vivo* as *in vitro*? 3) What is the most effective level of penicillin in the blood stream? The aid of the laboratory is essential in assessing the action of antibiotics, but the results of the laboratory tests must not be applied too rigidly in the treatment of disease.

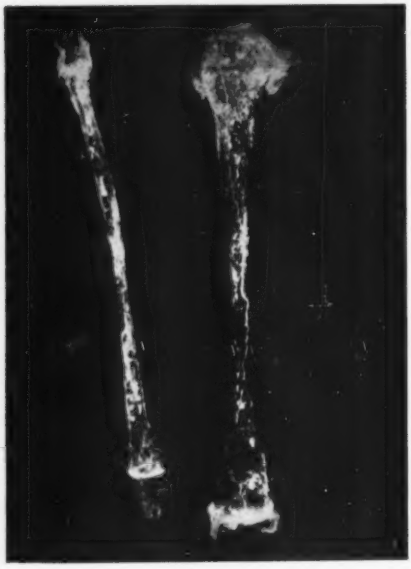

FIG. 14

Radiograph of decalcified tibia and fibula from an infant of three months. Vessels injected with a suspension of mercury in turpentine. The periosteum has been removed.

By aspiration of the infected marrow, McAdam (1945) showed that neither the temperature chart nor the leucocyte count was a reliable criterion of the time of sterilization of infected bone. After considerable hesitation we decided that repeated marrow puncture was the only method by which we could obtain some idea of the state of the metaphysis. In two of the early cases, penicillin-sensitive staphylococci were grown from the marrow after thirty-eight and twenty-eight days of what was considered adequate penicillin therapy (Dennison 1952*b*).

Absence of a therapeutic level of penicillin in the marrow on one occasion may be due to an error in technique. A repeatedly negative level combined with the growth of penicillin-sensitive staphylococci indicates interference with the blood supply. The detailed blood supply to the long bone of a child is difficult to demonstrate (Fig. 14) but it is probable that the distribution of vessels as described by Lexer (1903) and Johnson (1927) is reasonably accurate. Interference with this blood supply (Fig. 15) prevents the distribution of penicillin to the metaphysial focus. In such cases it is our custom to drill several holes in the metaphysial region. This allows local instillation of penicillin and, by the later

downgrowth of granulation tissue, probably provides an alternative blood supply to the metaphysis.

So long as patients continue to arrive in hospital with pus already formed, surgical intervention will continue to be necessary. But the methods of surgery described in Groups I and II of the present series have no place in the modern treatment of acute osteitis, and surgery has now become the handmaiden of penicillin. Bone drilling should rarely be adopted as a primary operation, but less harm will be caused by drilling followed by primary suture than by incomplete relief of tension.

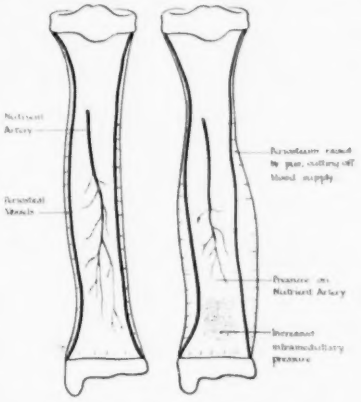
Nutrient Artery
Periosteum raised by pus, cutting off blood supply
Pressure on Nutrient Artery
Increased intramedullary pressure

FIG. 15

Diagrams to show how raising of the periosteum cuts off blood supply to the outer cortex. Diagram on left shows normal condition. That on right shows conditions in osteitis with pus formation. Periosteum has been raised, and increased intramedullary pressure has occluded branches of the nutrient artery. Thrombosis may lead to death of large areas of metaphysis and shaft.

Results—To those of us who were called upon to treat acute haematogenous osteitis before the introduction of penicillin, it is obvious that we are now working in a new era (Wilkinson 1951). During the period under review more and more attention has been given to maintenance of fluid and electrolyte balance. By 1936 intravenous therapy had replaced the subcutaneous and rectal routes in maintaining normal fluid balance and during the war years plasma became available and gradually replaced or supplemented glucose-saline. These factors must be taken into consideration when assessing the results of chemotherapy and antibiotics. The decline in mortality figures in the successive groups of cases has already been mentioned. On the other hand improvement in the morbidity rate is more difficult to demonstrate. Some indication of the reduced morbidity is given in Figures 5 to 7, which show the duration of hospital treatment in the three groups. Although metastatic lesions have become rare, the single case of pericarditis in Group III is a reminder that penicillin has not lessened our responsibility for thorough examination and precise diagnosis. An increasing incidence of penicillin-resistant staphylococci has been reported from many centres but apart from neonatal cases these organisms are still rare in the surgical division of this hospital. One acute bone infection caused by a penicillin-resistant staphylococcus ended fatally. The newer antibiotics should prevent the repetition of such a tragedy. Delay in evacuation of pus, inadequate penicillin dosage or insufficient duration of treatment may all lead to cavitation or sequestrum formation and, if these conditions are not treated early, to limb lengthening. Sequestra, if sterilised, will be absorbed. Coagulase-positive staphylococci have been cultured from all sequestra that required surgical removal. In spite of the increased attention that is being paid to the teaching of paediatrics, it is regrettable that patients in Group III were brought for treatment even later than those in the two earlier groups.

It should be remembered that there has been an improvement in the general management of paediatric cases in the period under review. When assessing the beneficial results of chemotherapy and antibiotics in osteitis we must consider the contribution made by this factor, which is attributable partly to an increase in the number of those who devote the main part of their time to the problems of surgery and anaesthesia in childhood. The paediatric surgeons and anaesthetists work in close collaboration with their medical colleagues and meet them in a much wider common field than exists for those who work only with adults. Consequently there has been more detailed pre-operative and post-operative care, particularly in the maintenance of normal fluid and electrolytic balance.

SUMMARY

1. Two hundred and twelve cases of acute haematogenous osteitis treated between 1936 and 1950 have been reviewed.
2. The cases are described in three groups: Group I—Seventy-five cases treated before the introduction of effective chemotherapy; Group II—Fifty-five cases treated with sulphathiazole and Group III—Eighty-two cases treated with penicillin.
3. The problems of penicillin therapy are discussed.

We wish to thank Dr Alistair M. MacDonald and his colleagues for their inestimable help with pathological problems and we are grateful to Dr D. Campbell Suttie for his help in the interpretation of radiographs. The photographs are the work of Mr J. L. A. Evatt.

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POSTERIOR DISLOCATION OF THE SHOULDER

Report of Six Cases

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In *A Treatise on Dislocations and Fractures of the Joints*, Sir Astley Cooper described nine cases of "dislocation of the os humeri on the dorsum scapulae." In eight of these the diagnosis was made before reduction. Astley Cooper wrote: "It is an accident which cannot be mistaken, as there is a protuberance formed by the bone upon the scapula which immediately strikes the eye; and when the elbow is rotated the protuberance rolls also. The dislocated head of the bone may be easily grasped between the fingers, and be distinctly felt resting below the spine of the scapula; the motions of the arm are impaired, but not to the same extent as in either of the other states of luxation."

Posterior dislocation of the shoulder is only briefly described in modern text-books, and most writers emphasise the difficulties of the diagnosis and the frequency with which the condition is overlooked. This is ascribed partly to its infrequent occurrence and partly to the fact that the displaced humeral head is sometimes shielded by the acromion and not easily felt (Key and Conwell 1942). Swelling may also obscure the signs. Diagnosis has often depended upon radiographic examination. Even here there are difficulties if only the routine antero-posterior view of the shoulder is used; and Warrick (1948) has emphasised the value of the vertical projection, with the tube in the axilla and the cassette above the shoulder. In most cases the arm can be abducted sufficiently for this projection.

In this paper are recorded six cases of posterior dislocation of the shoulder, in four of which the diagnosis was made by clinical examination. Radiography was inconclusive until the vertical projection was employed. In two patients the posterior dislocation was not diagnosed at the first examination and, although the antero-posterior radiograph suggested an abnormality of the joint, a vertical view was necessary to confirm the diagnosis.

MECHANISM OF INJURY AND METHOD OF REDUCTION

Posterior dislocation of the shoulder is generally the result of direct violence—usually by a blow on the front of the shoulder, or a fall on to the hand with the arm flexed and adducted at the shoulder. In two of the patients there was a clear history of a direct blow on the shoulder; and in another the degree of bruising of the front of the shoulder suggested the same mechanism. An associated fracture of the head or greater tuberosity of the humerus has frequently been described, and was present in four of the patients.

Astley Cooper described several methods of reduction, using either simple traction on the arm, or abduction of the arm to 90 degrees, followed by lateral rotation. Most modern authorities recommend traction with adduction, assisted if necessary by direct pressure upon the displaced head (Jones 1926, Key and Conwell 1942, Watson-Jones 1943).

In five of the patients reduction was easy; but in the sixth it was difficult and, when achieved, was unstable. This difficulty was attributed to a loose fragment from the humeral head displaced within the joint.

CASE REPORTS

Case 1—A man aged thirty-three years was admitted to hospital for investigation of epileptiform attacks of recent onset. The last of these had occurred five weeks before, but no details were obtainable. On recovering consciousness the patient had found that his right shoulder was painful

and that his right arm was strongly adducted. Movements of the hand and forearm were normal. During the period between the fit and his admission to hospital he had endeavoured to increase the range of movement of his shoulder by active exercises, but with little success.

Examination—The right arm was held in adduction and medial rotation, and the normal contour of the shoulder was lost. Abduction at the scapulo-humeral joint was limited to 5 degrees, flexion to 20 degrees and extension to 10 degrees; there was no lateral rotation. There was no wasting or paralysis of the muscles of the shoulder or of the arm, and no sensory or vascular abnormalities. A clinical diagnosis of posterior dislocation of the shoulder was made.

Radiographs—The antero-posterior view of the right shoulder showed an abnormal relationship of the humeral head to the glenoid (Fig. 1). A view taken with the x-ray tube in the axilla and the cassette placed above the shoulder showed a posterior dislocation of the head of the humerus, and a fracture of the greater tuberosity (Fig. 2).

Treatment—The shoulder was manipulated under general anaesthesia and the dislocation reduced. The arm was immobilised on an abduction splint with the shoulder abducted 90 degrees. One

FIG. 1

FIG. 2

Case 1—Posterior dislocation with fracture of greater tuberosity.

month later, active exercises were begun, and within the next three months the patient had regained a good range of painless movement (abduction 120 degrees, flexion 145 degrees, medial rotation 50 degrees and lateral rotation 20 degrees). This has since increased almost to a normal range.

Case 2—A linesman aged fifty-five years complained of pain in the left shoulder. On the previous day he had suffered a severe electric shock which had thrown him to the ground and had caused a burn of the left forearm. He stated that he fell on to his left side on a hard surface, but he was unable to give any further details of the accident.

Examination—There was no loss of contour of the shoulder, but all movements were restricted. The localisation of pain and tenderness led to a diagnosis of rupture of the long head of the biceps. Antero-posterior radiography of the shoulder suggested an abnormality of the position of the head of the humerus but was not conclusive (Fig. 3). The shoulder was treated by rest in a collar-and-cuff sling. At a further examination one week later a vertical radiograph of the shoulder was taken (Fig. 4), and showed a posterior dislocation of the head of the humerus.

Treatment—Manipulative reduction was performed the same day, and the arm was immobilised in a sling. Active movements were begun after three weeks, and six weeks later there was almost a full range of movement in all directions, with only slight pain on full abduction.

Case 3—A schoolmaster of thirty-one years complained of severe pain in the left shoulder shortly after an accident in which he had struck the front of his left shoulder on the road.

Examination—The left arm was held adducted and medially rotated. The contour of the left shoulder appeared normal, but deep palpation revealed a hard mass posteriorly, below the spine of the scapula. There was diffuse tenderness over the whole shoulder area and all movements were severely restricted by pain. There was no nerve or vascular injury. A clinical diagnosis of

FIG. 3

FIG. 4

Case 2—Initial routine antero-posterior radiograph (Fig. 3) was inconclusive, and the diagnosis of posterior dislocation was missed until the vertical projection (Fig. 4) was obtained.

FIG. 5

FIG. 6

Case 3—Posterior dislocation with fracture of humeral head.

posterior dislocation of the shoulder was made, and the mass felt posteriorly was presumed to be the displaced humeral head.

Radiography—The antero-posterior radiograph of the left shoulder showed a fracture of the head of the humerus, which was not lying in its normal relationship with the glenoid (Fig. 5). The

vertical projection showed a comminuted fracture of the humeral head, and a posterior dislocation (Fig. 6).

Treatment—The dislocation was reduced without difficulty under general anaesthesia. The arm was supported in a sling and bandaged to the chest. After three weeks, active movements were begun. Two months later movements of the shoulder were as follows: abduction 75 degrees, flexion 120 degrees, medial rotation full, lateral rotation 45 degrees. He failed to attend for further examination.

Case 4—A gardener of forty-two years was admitted after a motor cycle accident in which he had injured his left shoulder. He was unable to give exact details of the injury.

Examination—The normal contour of the left shoulder was lost and there was acute tenderness over the posterior surface of the joint, where the dislocated head of the humerus was palpable. There was evidence of an injury to the axillary nerve.

Radiography—Antero-posterior radiography suggested an abnormality of the position of the humeral head and showed a fracture of the greater tuberosity, with a loose fragment of bone in the joint. A vertical projection showed a posterior dislocation of the humeral head (Fig. 7).

FIG. 7

FIG. 8

Case 4. Figure 7—Before attempted reduction. Figure 8—After reduction. Anterior fragments of the head still displaced.

Treatment—The dislocation was reduced with difficulty under general anaesthesia but the reduction was unstable. A vertical radiograph after reduction (Fig. 8) showed that the greater part of the head was articulating with the glenoid, but that two large fragments had been fractured from the head anteriorly, and were still displaced. It was decided to accept this position, and the arm was supported in a sling with a bandage fixing it to the chest.

Recovery was complicated by the formation of a large haematoma around the shoulder and by severe pain. Active movements of the shoulder were begun four weeks after reduction, but recovery of movement was slow and after a further two weeks passive abduction was still limited to 50 degrees, and lateral rotation was possible only to 40 degrees short of the neutral position. As the deltoid paralysis showed no evidence of recovery the arm was supported on an abduction splint. During the next four months the nerve lesion recovered, but the range of movement of the shoulder failed to improve. Five months after the injury the joint was explored through an anterior incision and a large mass of new bone and fibrous tissue was excised. The subscapularis muscle was divided close to its insertion and the shoulder could then be abducted passively to more than 90 degrees. This improved range was maintained after the operation and when last seen the patient could abduct his arm actively and without pain to 80 degrees and could rotate laterally to within 10 degrees of the neutral position.

Case 5—A farmer of seventy-six years attended for examination a few hours after injuring his left shoulder in a fall.

Examination—The shoulder appeared to be flattened, and the head of the humerus was easily

FIG. 9

Case 5—Incongruity of articular surfaces, with fragment separated from humeral head.

FIG. 10

FIG. 11

Case 6—Initial antero-posterior radiograph had been reported as normal, but these further films showed posterior dislocation.

palpable below the acromion. The coracoid process felt unduly prominent. The arm could be adducted and rotated medially without difficulty, but lateral rotation was impossible.

Radiography—Antero-posterior views only were taken in this case, and showed that the humerus

was rotated at the shoulder and that the humeral head was displaced from the glenoid cavity. A fragment of bone was seen to have been fractured from the humerus, presumably from the greater tuberosity (Fig. 9).

Treatment—The dislocation was reduced without difficulty under general anaesthesia. Active exercises were begun three weeks from the date of reduction. Four weeks later the patient had recovered almost a full range of active movement, but abduction remained rather weak.

Case 6—A man of forty-two years attended hospital after being knocked down by a car. The details of the accident were not available, but he had suffered a head injury, and on account of this he was admitted. Not until two days later did he complain of pain in the left shoulder.

Examination—All movements of the shoulder were restricted, but no further clinical signs were noted and a diagnosis of contusion of the shoulder was made. An antero-posterior radiograph was reported as showing no bone injury, and physiotherapy was ordered. Re-examination of the shoulder two days later suggested the possibility of a posterior dislocation.

Radiography—Further radiographs, including an axillary projection, showed a posterior dislocation (Figs. 10 and 11).

Treatment—The dislocation was reduced without difficulty under general anaesthesia. Subsequent progress was satisfactory and when seen six weeks later the patient had regained active abduction to 90 degrees, lateral rotation to 40 degrees and medial rotation to 90 degrees. He did not attend for further examination.

SUMMARY

1. Six cases of posterior dislocation of the shoulder are described.

2. In four cases the diagnosis was made on clinical grounds.

3. The important clinical signs are the adducted and medially rotated position of the arm, a hard mass posteriorly below the acromion representing the displaced humeral head, and limitation of movement, especially abduction and lateral rotation.

4. In two cases the dislocation was not recognised at the first examination. This confirms the statement of previous authors that posterior dislocation is easily missed.

5. The value of the vertical projection in the radiography of suspected posterior dislocation is emphasised.

6. Reduction was accomplished without difficulty in five cases and the subsequent progress of these was uneventful. In the remaining case reduction was difficult and unstable, and the final recovery incomplete. It is considered that this patient would have been better treated by early open reduction.

We are indebted to Professor J. Trueta for permission to include Case 1; to Mr G. P. Arden for the records of Case 6; and to Mr J. C. Scott for permission to report the remaining cases which were treated in the accident service of the Radcliffe Infirmary, Oxford.

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MAN WITH THREE LEGS*

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In the autumn of 1948 a message was received from a rural practitioner stating that in the course of a visit he had discovered a man who, from the cursory glance that had been permitted, had a large sacral appendage with the appearance of a massive tail.

In the quiet of a Sunday morning a few days later one of us (I. S. S.) accompanied the doctor to an isolated cottage in a clearing in a wood, some considerable distance up a rough

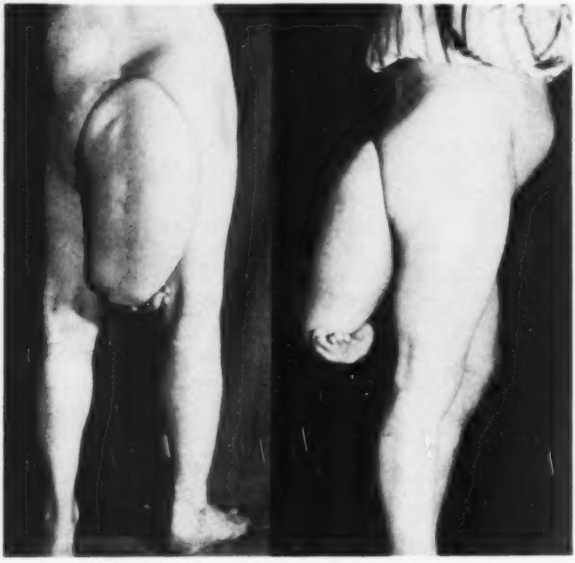

Fig. 1 Fig. 2

Figure 1—Third leg: posterior aspect. Figure 2—Third leg: right lateral aspect to show relationship of foot to thigh.

track from the main road. In a dimly lit room at the top of a narrow stair lay a middle-aged man with a beard and long black hair. He exposed the lower end of what he referred to as " the thing " reluctantly, slowly drawing up a thick flannel nightgown. He had never shown it to anyone before, not even to his own brother. The first impression, as he lay on his side with his back to the wall, was that of a tail supported by a hand (Fig. 1), but when he grudgingly allowed us to look more closely we discovered to our astonishment that what had appeared to be his hand was a mal-formed foot (Fig. 2).

He inquired gruffly if " the thing " could be removed. It was clear that the circumstances, in spite of inadequate examination, demanded a confident reply. A hospital bed was offered and accepted. There was one condition: he reminded us that he was about to make his first

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contact with the outside world; he must have a room by himself. The journey to hospital was his first sight of a main road and his first experience of a motor vehicle. His mind-picture of modern transport apparently differed from reality. He was sadly disillusioned by the journey.

History—The patient, aged fifty at the time of examination, was the youngest of six otherwise normal healthy children. When the abnormal infant was born, the doctor who was present recommended that the tumour be removed forthwith. Treatment, however, was firmly refused; the parents regarded the birth of a monster as a punishment for the sins of their forebears and a disgraceful episode in the family history which should be kept secret. The doctor was never permitted to see the boy again until he had almost reached adolescence. We were informed, with what truth we were unable to confirm, that an attempt to photograph him as a baby met with active hostility. With this knowledge our approach to a similar request fifty years later was delicate in the extreme.

His life had been one of complete seclusion. Until the age of ten he was concealed from view in a perambulator. From that time he is known to have run about freely, wearing a kilt. When the tumour outgrew the kilt, his parents clothed him in a dressing gown. The wearing of trousers was impossible. He came to hospital with the third limb bandaged to his right leg as was his practice, his infirmity concealed by a long skirt.

He received his early education from his brothers and sisters: his parents did not allow him to attend school. In spite of this background he might reasonably be described as an intelligent man with a surprising theoretical knowledge of the outside world, largely gained from books and radio. He had taught himself to repair watches and radio apparatus by which he said he earned a good living, but he neither saw his customers nor they him. He was almost aggressively boastful of his craftsmanship but he had no standards of comparison and it became clear, when the radio we loaned him for his entertainment broke down, that his abilities were limited to the repair of simple battery sets such as are used in country districts. His skill as a watchmaker remained untested.

He was regarded as a man of mystery in the Parish where he lived. Nobody had ever seen him at close range save the doctor and parson. The bearded figure wearing a skirt, seen occasionally in the woods at night, was the source of much speculation. He was the local bogyman.

As might be expected in a recluse with no contact with the rough and tumble of everyday life, he was of unshakable ideas and opinions. Statements contrary to his beliefs were regarded with contempt and he became a source of irritation to the nurses who looked after him. Further information regarding his personality would have been desirable but it was evident from his attitude to our questions that the attentions of a psychologist, however discreet, would be unwelcome and might have defeated the purpose for which the patient entered hospital.

When his parents died, three of the family were left at home—a brother, ten years his senior, and a sister, who kept house for them. The sister died five years previously and since then he had given much thought as to his predicament should his brother also die, leaving him to fend for himself. His concern was deepened by the fact that his brother suffered from pernicious anaemia and might well die before he did. This was the motive for his consulting the doctor who called at the cottage to attend his brother.

The pre-operative photograph was obtained after explaining that it was essential to the plan of treatment. In the numerous contacts necessitated by the unsavoury task of preparing his skin we thought that we had gained his confidence, but what we considered to be a tactful suggestion that the opportunity to change his personality and celebrate his successful treatment by a shave and a hair-cut was received in silence and disregarded. When he left hospital, wearing trousers for the first time, he showed neither pleasure nor gratitude for his return to normality. The post-operative photograph was secured at the second attempt and only after angry words and our accusations of ungracious behaviour.

Description of the appendage—The additional limb took origin from the right side of the mid-line in the gluteal region. The base, centred two and a half inches from the natal cleft, was seventeen inches in circumference. The total length, excluding the lower leg and foot, was seventeen inches. The mass was roughly the shape of a thigh, broadening to a maximum circumference of twenty-one inches and narrowing toward the distal end from which a very short curved lower leg, seven inches in length, projected at right angles to the anterior aspect. The leg encircled the distal end of the thigh on the medial aspect, and to it was attached a completely inverted foot possessing a well-formed heel and five normal toes with nails. A long slender accessory toe without a nail grew from the side of the first metatarsal (Fig. 3).

On the antero-medial aspect of the mass, between five and eight and a half inches from the superior boundary of the base, was an area of loose, wrinkled, hair-covered scrotal skin with a raphe from which a penis, the subject of a bifid glans and hypospadias, protruded

FIG. 3
Amputated leg showing curved tibia and foot with accessory first metatarsal.

FIG. 4
Amputated leg showing curved tibia, heel and external genitalia.

(Fig. 4). There was a doubtful urethral orifice at the base of a funnel of skin, five inches from the extremity of the glans. The root of the additional organ extended up to a rudimentary pubis which could be palpated immediately to the right of the anus. No testes were present; no secretions were ever discharged. It did, however, undergo erection concomitantly with the normally placed organ.

There was no voluntary movement in the limb. Sensation of a superficial character was present in the basal region, diminishing distally; there was no sensation in the foot.

Radiographs showed that the base of the limb included a rudimentary pubis and ischium. Articulating with this hemipelvis was a femur which ended distally in bony ankylosis with a malformed curved tibia (Fig. 5). Neither patella nor fibula was present. The tarsus was represented by a fused mass of bones. The metatarsals and phalanges were normally developed but with the addition of an accessory first metatarsal.

General investigation—Before operation several unsuccessful attempts were made to establish a possible communication between the rudimentary penis and the pelvic organs. Intravenous pyelography revealed two normally secreting kidneys, and a posterior diverticulum of the bladder which was also displayed by retrograde cystography.

Radiographs of the chest revealed a large mass in the anterior mediastinum displacing the heart and trachea to the left. In spite of the superficial position we speculated on the possibility of a second tumour in the form of a mediastinal teratoma but it was proved later that the tumour was a very large intrathoracic goitre arising from the right lobe of the thyroid gland.

FIG. 5

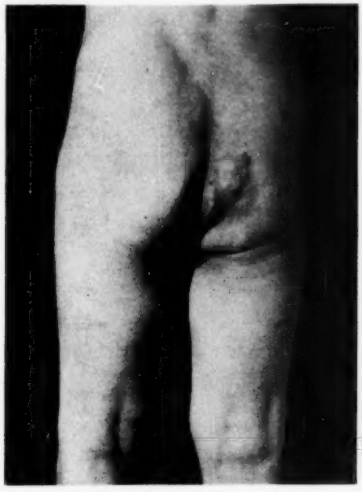

FIG. 6
Result of operation.

FIG. 5
Radiograph of amputated leg showing hemipelvis, femur, curved tibia and foot.

Operation—If any difficulty could be claimed in accomplishing removal of the limb it was in gaining access to the whole circumference of the base for pre-operative preparation of the skin, and then in fashioning suitable skin flaps. The operation itself consisted of little more than careful dissection through fibro-fatty tissue lest some unanticipated bowel, bladder or urethral element be encountered. No nerve or vessel of significant size was noted. The wound was drained for twenty-four hours and it healed in fourteen days. The patient was discharged from hospital one week later (Fig. 6).

Postscript—In spite of our hopes to the contrary, it became evident that this unfortunate man had lived too long with his tumour to change his ways. He returned to his room and to his watches, and was not seen outside the house. Whatever plans he may have had for the

future, his new-found freedom was shortlived. He died unexpectedly at his home three months after discharge from hospital from an acute infection of the urinary tract.

At post-mortem examination the bladder was found to be full of pus and the mucous membrane, especially of the posterior diverticulum, was acutely inflamed. A scirrhus carcinoma of the prostate invading the base of the bladder was found on section. There was no evidence of an additional urethra, nor indeed of any other embryological abnormality. The right lobe of the thyroid was markedly enlarged and it was located in the anterior mediastinum.

PREVIOUS RECORDS

Many congenital anomalies have as their origin deficiencies in, or arrest of, the normal process of uniovular twin formation. These range from Siamese twins and double-headed monsters to infants with additional legs, pelves, internal organs and arms. Less well-defined evidence of attempts at twinning at various levels in the embryonic axis are represented by sacro-coccygeal tumours and teratomas of the mediastinum or palate.

The strong tendency which exists in both vegetable and animal kingdoms for parts ending in free extremities to bifurcate or dichotomise takes the form in the human species of the additional fingers or toes which are the common experience of every orthopaedic surgeon. Examples of dichotomy of the lower limb bud resulting in an additional hemipelvis, leg and external genitalia are, however, extremely rare. It appears that there are only twenty to thirty recorded cases which bear any resemblance to the one we have described. Most of those traced are collected in Gould and Pyle's *Anomalies and Curiosities of Medicine*. The exact number is in doubt. In some instances the same case has been described by two or more observers; in others an early writer, having described a case, claims to have seen "several more." Furthermore it is clear that the older writers, perhaps the best example being Ambroise Paré, were permitted a greater degree of artistic licence than is currently acceptable.

In two instances duplication of all parts below the upper lumbar region has been described (Heschl 1878, Wells 1888); in three there was duplication of both arms and legs (Paré 1598 two cases, and Bardsley 1838); and in four there was duplication of both legs (Aldrovandus 1646–48, Geoffroy-Saint-Hilaire 1830, Gould and Pyle 1898 two cases, one shown by a midwife, Académie de Sciences, Paris 1830, and Louise L, known as "*la dame à quatre jambes*," born 1869). In four cases it is clear that the appendage represented a pair of legs which had failed to divide (Amman 1670, Geoffroy-Saint-Hilaire date unknown, Guérin 1894, Gould and Pyle 1898). The remainder had a single extra limb, many with additional features such as duplication of pelvic organs, external genitalia and mammary glands (Plancus 1749, Haller 17— exact date unknown, Dumeril 1801, Goré 1844, Bechlinger 1888, Jones and Larkin 1889, Tucker 1895, Gould and Pyle 1898, patient born 1860, possibly the same as the one quoted by Bechlinger, Zammit 1898, Deboo 1943).

Two of the cases recorded above bear a marked similarity to our case. Zammit, in 1898, described a Sicilian boy with an extra right leg who, however, had active muscular control of both hip and knee joints; and Deboo, in 1943, described an Indian boy with an extra leg and hemipelvis having its root situated between the pubic bones who, however, had two urethrae leading from a single bladder.

SUMMARY

1. The extraordinary background and circumstances of discovery of a man, aged fifty, the subject of the rare congenital anomaly of posterior dichotomy, taking the form of a hemipelvis and complete lower limb is reported.

2. The appendage is described and illustrated.

3. Investigations and treatment are described and the result illustrated.
4. Reference is made to previous recorded cases in the literature.

We are indebted to Dr R. S. Edington, who referred the patient, and to Dr J. Liddell who was present at the birth of the abnormal infant, for the assistance they have given in reconstructing the history.

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OPEN DISLOCATION OF THE ELBOW WITH RUPTURE OF THE BRACHIAL ARTERY

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A search of the literature has revealed only one report in Britain of posterior dislocation of the elbow complicated by rupture of the brachial artery. This was a closed injury (Marnham 1934). In America, Cotton (1924) described the complication of arterial rupture as "excessively rare and compound mainly." Eliason and Brown (1937) collected twenty-one case records of posterior dislocation of the elbow with arterial damage. Sixteen of these were open injuries and in fifteen the brachial artery was found divided. In the remainder, the

FIG. 1

FIG. 2

FIG. 3

Case 1. Figure 1—Drawing of elbow before operation. Figure 2—Radiograph before operation. Posterior dislocation of elbow with detachment of medial epicondyle. Figure 3—Condition one month after operation.

radial and ulnar arteries were ruptured. Out of these twenty-one cases, only five gave good functional results. This paper reports two cases of open posterior dislocation with arterial rupture, one of which was further complicated by closed fractures of both bones of the forearm.

Case 1—A boy aged thirteen years was admitted after a fall from a gymnastic "horse." His general condition was good. The left elbow was held fully extended and, protruding through a small wound in the antecubital fossa, was seen the lower end of the humerus, denuded of all soft tissues (Fig. 1). The hand was pale and cold, and pulses at the wrist could not be felt. Radiographs showed, in addition to posterior dislocation of the elbow, a fracture of the medial epicondyle (Fig. 2). At operation, the edges of a small longitudinal wound were excised and the opening extended proximally and distally. Lying in front of the retracted brachialis muscle, the proximal cut end of the brachial artery was found sealed off and pulsating. The distal cut end was found lying under cover of the humerus. Both were ligated. The ulnar nerve lay across the olecranon fossa. Median and radial nerves were not seen. By combined flexion of the elbow and traction on the forearm the dislocation

was reduced (Fig. 3). The ulnar nerve was transposed anteriorly and the medial epicondyle, with its attached flexor origin, was reattached with a few sutures and the wound closed.

After operation, radial and ulnar pulses returned within forty-eight hours. A partial wrist drop recovered in less than two weeks. After four weeks, active movements were begun. One year later elbow movements and power were full.

Case 2—A boy aged nineteen years was admitted after a fall from a tree on to his outstretched right hand. From a ragged, transverse wound in front of his right elbow was seen protruding the lower end of the humerus. In the forearm, the clinical appearance of closed fractures of radius and ulna, at junction of lower and middle thirds, was confirmed by radiographs (Fig. 4). Pulses could not be felt at the wrist. At operation the wound was excised. The only structure lying in front of the humerus was identified as the median nerve. The cut ends of the brachial artery, separated by a gap of four centimetres, were found under the wound edges and ligated. The ulnar nerve was not seen. The dislocation was reduced and the wound closed. An attempt to reduce the forearm fractures by manipulation was rendered difficult by the instability of the elbow. Circulation returned to the hand within forty-eight hours and there were no signs of median or ulnar nerve injury. Three weeks later, open reduction of the forearm fractures was carried out, fixation being maintained by stainless steel plates. Immobilisation by plaster was deferred, and active movements of the elbow were encouraged for three weeks. Then a close-fitting full arm plaster was applied. After ten weeks both fractures had united and active movements were resumed. The condition one year after the injury is shown in Figure 5. Movements and power of elbow and wrist were almost full.

FIG. 4

FIG. 5

Case 2. Figure 4—Before operation. Dislocation of elbow with fractures of radius and ulna. Figure 5—Condition one year after operation.

We should like to thank Mr S. L. Higgs for permission to publish the first case, Dr W. J. Wright for his drawing at operation and Mr R. G. Whitley of the Institute of Orthopaedics for his help with the reproductions.

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A RING-SHAPED MEDIAL SEMILUNAR CARTILAGE

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During classroom dissecting, students found an abnormal medial semilunar cartilage in the left knee of a male subject. This man had died at the age of fifty-four of bronchopneumonia. There was no mention in the hospital history of injury to his left knee, but there was a history and anatomical evidence of fracture of his right leg eight years before death. There was no abnormality apparent in the right knee.

Description of specimen—At first glance, it appears that the medial meniscus, instead of occupying its usual position, is reversed or folded over to the intercondylar area. In reality, the medial meniscus forms a ring of fibrocartilage which is much wider and thicker laterally. Posteriorly the ring is firmly attached to the area where a normal posterior horn would be. In front of and behind this attachment the convex edge of the ring is unattached for almost two inches and one inch respectively. In the drawing (Fig. 1) this has been illustrated by the inserted paper strips. The remainder of the convex edge is attached to the capsule, but there is no mooring to bone anteriorly—that is, there is no anterior horn. The concave edge is free and regular and tapers to a sharp edge like normal meniscus. All the joint surfaces of the bones—femur, tibia and patella—appear to be normal.

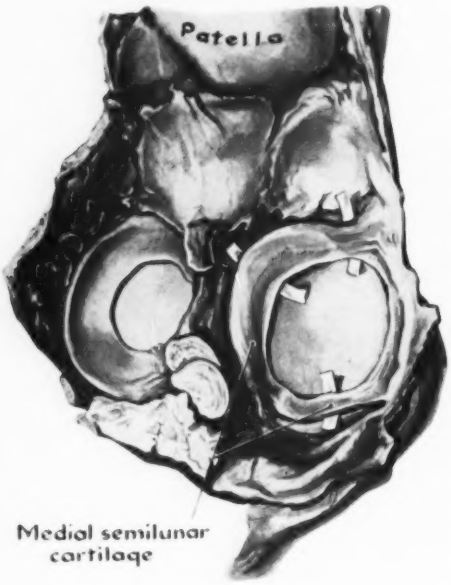

Fig. 1

Discussion—Is the abnormality described developmental or traumatic? If developmental, is it an atavism or is it an arrest of normal human growth? A search of the literature resulted in the following findings and conclusions. Examples of disc-shaped *lateral* semilunar cartilage, first described by Young in 1889, have been reported by Higgins (1895), Fisher (1924), Duncan (1932), Ellis (1932), Bristow (1935), Jaroschy (1935), Fairbank (1937), Middleton (1936) and Smillie (1946). Two papers, the first by Cave and Staples (1941), the second by Dwyer and Taylor (1945), have described single cases of disc-shaped *medial* semilunar cartilage and a third case was described by Smillie (1946), who also reported nineteen cases of discoid lateral cartilage. In 1937 a case of reversed lateral cartilage was described by Fairbank in a child. The only case of a ring-shaped medial cartilage previously reported was described by Watson-Jones in 1939, and he, too, was uncertain about the etiology. Otherwise there are vague references in the literature to the rare occurrence of the condition with no authentic reports. Undoubtedly, anomalies of the medial cartilage are rare.

Comparative anatomy sheds no light on our problem. This is well demonstrated in the

early work of Parsons (1900), confirmed by Herzmark (1938), Jaroschy (1935) and McDermott (1943). The medial semilunar cartilage in all primates, and in many other mammals, has an appearance very much like that in man, although the lateral cartilage does form a complete ring in various monkeys (macacus rhesus). It is interesting to note that, although no mammal has a plate-like lateral cartilage, writers have invoked teleology in explaining the rare occurrence of this anomaly in man, giving as proof the cartilages of the lizard.

At no stage of the human embryo is the medial cartilage ring-shaped or reversed. McDermott (1943), McMurray (1942) and others have found that the cartilages develop from primitive mesenchyme or blastema which rapidly becomes specialised. One could imagine an anomaly developing in the earliest phases, but surely that is not atavism.

Surgeons would suggest that the abnormality here described is a bucket-handle tear with gross displacement of the fragment into the intercondylar notch. MacAusland (1943), in his analysis of a large series of injured cartilages, described and showed illustrations of such bucket-handle tears. In the opinion of Professor R. I. Harris, the present case " represents a bucket-handled tear which has been completely displaced into the intercondylar notch for a long time—long enough to iron out the anterior and posterior points of junction of the separated free margin with the cartilage proper." Admitting this to be a very real possibility, I cannot locate any good illustration or description of an authentic fractured medial cartilage with the same appearance. The question " is it developmental or is it traumatic ? " appears to remain unanswered.

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EWING'S TUMOUR AFFECTING THE MEDIAL CUNEIFORM BONE

Report of a Case

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The characteristic radiographic appearances of Ewing's tumour in a long bone are well known, but it is not so generally realised that the changes that occur when a short bone is affected are quite different and by no means typical. For this reason the following case is thought to be worth recording.

A boy of fourteen complained of pain in his left foot which developed after a kick and which had been present for about six months. There was no obvious deformity of the foot and all movements were full, but there was slight oedema and increased warmth on the medial aspect of the middle of the foot. The radiographic appearances are shown in Figure 1.

It was considered that the condition was probably a low grade infection of the medial cuneiform bone, but because the diagnosis was uncertain a biopsy was performed. The medial cuneiform bone was exposed and a small hole made in the cortex. The interior of the bone contained grey semi-solid material which was scooped out. The histological appearances were reported as being those of Ewing's tumour (Professor H. L. Sheehan and Professor S. L. Baker). Amputation below the knee was performed. Pathological examination of the specimen confirmed the previous histological findings (Figs. 2 and 3).

FIG. 1
Clinical radiograph of left foot.

The patient remained well for two years, but at that time evidence of pulmonary metastases was found on radiographic examination. He died just over three years after the amputation. Permission for necropsy could not be obtained.

DISCUSSION

The chief interest of this case centres round the interpretation of the histological appearances. Sections from the amputated specimen were submitted to Professor H. L. Sheehan, of the Department of Pathology, University of Liverpool; to Professor R. A. Willis, of the Department of Pathology, University of Leeds; and to Professor S. L. Baker, Professor of Pathology in the University of Manchester. Professor Sheehan, who had reported on the biopsy specimen, discussed the appearances of the amputated specimen as follows: " The amputation specimen slides support the diagnosis of sarcoma quite unequivocally. But is it a Ewing's tumour ? This brings up the question of what is meant by a Ewing's tumour. There is considerable doubt as to whether it is a pathological entity. It seems easier to take the three aspects: 1) Clinically a picture of subacute osteomyelitis, commonly following trauma; usually in adolescent boys. 2) Very great radiosensitivity. 3) A histological picture with the general appearance of round-celled sarcoma, lymphosarcoma, neuroblastoma, undifferentiated carcinoma of bronchus, and the remaining tumours of this type. The nuclei are usually rather larger than those of lymphocytes; there is little cytoplasm. The tumour does not produce bone, does not destroy it much, and extends a long way up the marrow. The present case shows in places a certain tendency to

slightly oat-cell shape but in others is a round-celled type. I should accept it as having the same appearance as the general group of Ewing's tumour (or of the other tumours mentioned above). I doubt whether there is any specific histological appearance of Ewing's tumours so I should not like to be any more definite than that."

Professor Willis reported: "I agree that this is the kind of tumour which is commonly described as 'Ewing's tumour.' My views on this subject are epitomised in my book *Pathology of Tumours*, page 686. 'Ewing's tumour' is *not* a single pathological entity, but rather a

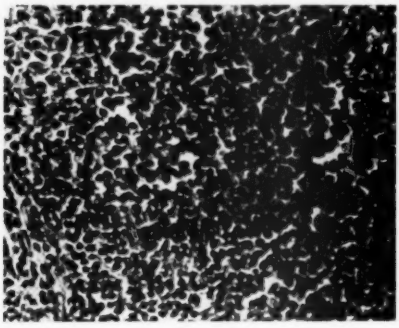

FIG. 2
Cellular part of the tumour.

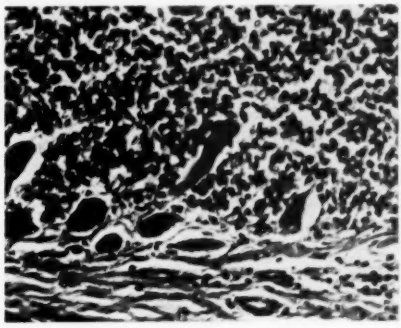

FIG. 3
Tumour invading muscle fibres.

clinical syndrome which can be produced by several different kinds of tumours. One of the most frequent of these in young subjects is metastatic neuroblastoma, from primary growths in the adrenals or sympathetic ganglia. These primary growths are often not discoverable clinically, and are to be found only by careful necropsy. In my opinion, the cytology of the tumour in Mr Roaf's case strongly suggests neuroblastoma, though rosette formation is not distinct enough to justify a dogmatic diagnosis. In Professor Baker's letter I see a footnote saying 'metastases now present.' If Mr Roaf can obtain a competent necropsy on the case, he may later be in a position to identify the tumour more precisely. Otherwise, its nature will remain uncertain."

Professor Baker reported as follows: "There is in my view no definite histological criterion by which a 'genuine Ewing' tumour can be recognised. Some pathologists are doubtful if Ewing's tumour is an entity at all. Personally, I report bone tumours of the kind seen here as 'Ewing type'—by which I mean an undifferentiated tumour composed of cells with little cytoplasm, and with fairly uniform oval or rounded nuclei, not bone-producing but apparently arising in bone. Tumours of this general histological type are radiosensitive whether they are primary in bone or arise elsewhere, so that this does not help in distinguishing a Ewing tumour from other tumours of similar histological type. Willis has reported several cases of neuroblastoma of the adrenal in which a bone deposit producing all the characters of a Ewing's tumour was the presenting feature clinically. In my collection of 'Ewing type' tumours, although they all conform to the general description given above, they have not identical histological appearances and probably represent a group with certain similarities and not a single definite entity. In Mr Roaf's case the tumour is certainly malignant and there seems a reasonable probability that it is a primary bone tumour belonging to this group. It would be an unusual site for a single secondary growth."

I wish to thank Professor Sheehan, Professor Willis and Professor Baker for their valuable assistance.

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FIBROSARCOMA OCCURRING IN A CHRONIC BONE SINUS

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Recent publications by Marks and Turner (1950) and Gillis and Lee (1951) have drawn attention to the occurrence of carcinoma in sinuses of osteomyelitis and as a sequel to war wounds. The case to be described is unusual because the tumour which grew rapidly in relation to a chronic bone sinus of forty-eight years duration proved to be a fungating fibrosarcoma. So far as can be ascertained no similar case has been reported in the British literature.

CASE REPORT

A man aged sixty-six years was admitted to hospital on account of a rapidly enlarging growth that had appeared three months previously on the outer side of the left thigh at the site of a chronic discharging sinus. In 1903, while in India, he had injured his left knee at football and the knee had been operated upon. Osteomyelitis developed and he was left with a chronic sinus on the outer surface of the left thigh, and a stiff knee. A further operation was undertaken in 1936 but the sinus continued to discharge. Shortly before admission he had had a rigor and developed a high fever. It was assumed that this was related to an acute flare of his osteomyelitis as no other cause could be found.

Fig. 1

Radiograph showing the changes in the lower end of the femur.

On examination, there was a fungating mass four inches in diameter with a base two inches wide at the site of the sinus (Fig. 2). The growth was heavily infected and bled easily but it felt firm. The left knee was ankylosed. The inguinal glands were not palpable.

Radiographs showed a large cavity in the lower end of the femur surrounded by sclerosed bone (Fig. 1). Periosteal new bone formation extended half way up the shaft of the femur. There was bony ankylosis of the knee joint. Radiographs of the chest were normal.

Investigations—Blood count showed haemoglobin 56 per cent and red blood corpuscles 2,460,000 per cubic millimetre. White cells numbered 17,800 per cubic millimetre of which 81 per cent were neutrophils. Blood urea was 56 milligrams per 100 millilitres.

Biopsy—A wedge-shaped piece of tissue was removed. Histological examination showed a cellular tumour composed mainly of spindle cells with scanty fibre formation. A thick network of reticulin was present and here and there a little collagen had been formed. There were numerous mitoses. The periphery of the growth was necrotic and infiltrated with leucocytes, but the central mass was free from inflammatory cellular infiltration. The conclusion of the pathologist was that the tumour was a growing fibrosarcoma.

FIG. 2

Photograph showing the gross appearance of the fungating tumour on the outer side of the left thigh.

FIG. 3

Photograph of the specimen after it had been divided longitudinally. This shows the extent of the tumour and the underlying abscess.

Treatment—After preliminary blood transfusion and a course of penicillin injections above-knee amputation was carried out.

Pathological examination—The tumour extended through the muscles into the femur (Fig. 3). There was an irregular osteomyelitic abscess in the lower end of the femur. The abscess contained a small sequestrum and was lined by necrotic material except on the medial side, where the growth extended into it through a breach in the cortex. Histological sections

(Figs. 4 and 5) showed the growth to be a sarcoma, the structure being similar to that of the biopsy material. It was composed mainly of spindle-celled tissue although other areas were more anaplastic and there was some necrosis. Spicules of degenerating bone were present around the edges and in one area there were a number of multinucleate giant cells which appeared to be osteoclasts. There was no formation of new bone or its precursors. There was no evidence to suggest that this sarcoma was osteogenic in nature. Presumably it had arisen from granulation tissue lining the sinus leading to the osteomyelitic abscess.

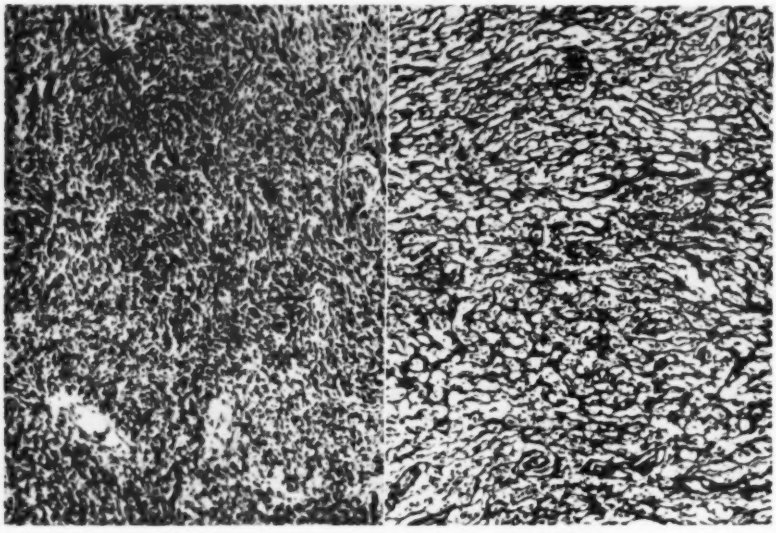

FIG. 4 FIG. 5

Figure 4—Photomicrograph of a representative field showing the cellularity of the tumour with scanty fibre formation (H. and E. × 70). Figure 5—Photomicrograph of a silver impregnation preparation to show the rich network of reticulin throughout the whole growth (× 120).

Progress—After amputation the patient's general condition improved rapidly. Two months later, however, he died suddenly after a short illness, with symptoms suggesting a severe gastro-intestinal haemorrhage. Consent for a post-mortem examination was not obtained.

DISCUSSION

Whereas carcinoma is a well recognised complication of a chronic bone sinus, the occurrence of a fibrosarcoma is unusual. Gillis and Lee (1951) mentioned that they had seen examples of sarcoma which appeared to have arisen in deeper tissues around scars and foreign bodies. But they did not report any case of sarcoma arising in relation to a chronic bone sinus. Cade (1951) remarked that the occurrence of fibrosarcoma as a sequel to war wounds was well known, but he did not elaborate on this statement or discuss fibrosarcoma occurring in chronic bone sinuses. The comparative rarity of this complication can be judged from the following figures: in approximately 4,000 cases of osteomyelitic sinuses studied at the Mayo Clinic, malignant changes were found in 0·23 per cent, but no sarcomata were reported (McAnally and Dockerty 1949). In one case the tumour was reported as a "grade 3 epithelioma and fibrosarcoma," but a review of other sections revealed that it was actually an epithelioma simulating a fibrosarcoma. Henderson and Swart (1936) reported one case of fibrosarcoma

arising in connection with a sinus. This tumour arose twenty-two years after the onset of osteomyelitis in the tibia. The limb was amputated and histologically the tumour was thought to be a fibrosarcoma, but four months later the inguinal glands were found to be enlarged and a biopsy of these revealed epidermoid carcinoma. This case, therefore, like that of McAnally and Dockerty, should be classified as a carcinoma, as the original histological interpretation is open to doubt.

Kirshbaum (1949) reported a case of osteomyelitis of the tibia of thirty-one years' standing. An ulcer and a mass developed at the site of the sinus. Amputation was undertaken and there was no recurrence in three years. Microscopy proved the tumour to be a fibrosarcoma. Geschickter (quoted by Kirshbaum 1949) described a similar case, but no details were given.

In the case reported above the clinical diagnosis was of a carcinoma, and the biopsy report of fibrosarcoma was unexpected. It is evident from the histological findings, which are illustrated in the accompanying photomicrographs, that the tumour arose from connective tissue and not from the epidermis.

Fungation of a fibrosarcoma through the skin is uncommon and is virtually seen only after a surgical incision for biopsy or removal. In this case, and in others described in association with sinuses, circumstances exist in which fungation might reasonably be expected.

No conclusion can be drawn from the few cases published as to the relative prognosis between epithelioma and sarcoma. The etiological factors and the natural history of the condition are probably very similar in each.

My thanks are due to Mr H. L.-C. Wood, under whose care the patient was, for his help and advice, and to Dr G. F. M. Hall of the Morbid Anatomy Department, King's College Hospital, for the pathological reports.

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EXPERIMENTAL CAUSATION OF CONGENITAL SKELETAL DEFECTS AND ITS SIGNIFICANCE IN ORTHOPAEDIC SURGERY*

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The frequency of anomalies of development is much greater than one would be inclined to suggest from an examination of the records of hospitals. According to Stockard (1909) congenital malformations of various types and degrees cause " the death of about 23 per cent of the human race before or shortly after the time of birth and handicap a certain proportion of the survivors throughout their lives." MacGregor (1946), who reviewed 1,053 stillbirths and neonatal deaths, found that 20 per cent of stillbirths and 10 per cent of neonatal deaths were directly attributable to gross congenital malformations. Mall's careful studies in 1908 led him to conclude that the great majority of aborted foetuses were malformed, and that out of every hundred pregnancies not more than eighty terminated in the birth of normal infants at full term.

The pathology of the human foetus is a relatively unexplored subject, though over half a century ago Ballantyne of Edinburgh (1895, 1904) made a notable beginning to the solution of at least some of its problems with his classical books: *The Diseases and Deformities of the Foetus* and *The Manual of Antenatal Pathology and Hygiene*. Since but little is known of the detailed histology of the early human embryo, histological examination in cases of perverted growth is limited mainly to aborted foetuses which, unfortunately, tend to present varying degrees of post-mortem degeneration before accurate histological methods can be applied. It is precisely in this field that experimental work can offer valuable help. According to Mall (1917) and others, the pathological changes that take place in human foetuses and those obtained experimentally in animals are not merely " analogous or similar but identical."

During the past few decades the discovery of genetic factors leading to congenital malformations has attracted a great deal of attention, while research in the field of environmental teratogenic factors has lagged behind. The importance of environmental causes of *human* malformations has not received as much emphasis as it should have done. From recently published surveys of the works on the subject (Macklin 1936, Murphy 1947, Steindler 1950) it might be concluded that abnormal genes are the cause of practically all congenital malformations. However, the association of developmental anomalies such as cataract, cardiac septal defects, patent ductus arteriosus, deaf-mutism, dental defects, and microcephaly with epidemics of rubella, noted first in Australia by Gregg (1941, 1945) and attributed to maternal infection in the early months of pregnancy by Swan and others (1946) demonstrates clearly enough that changes in the germplasm cannot always be invoked as the cause of congenital abnormalities. It will be of great interest to the geneticist to know that types of congenital malformations which are sometimes genetically determined, such as microphthalmos, cleft palate, and certain skeletal abnormalities, can be induced in the offspring not only by maternal nutritional deficiencies (Warkany and Nelson 1941) and by x-radiation (Bagg and Little 1924) but also, at least in some animals, by the deliberate introduction of certain substances such as insulin into the environment of the embryo during its development.

In 1943, while investigating the role of glycogen granules in hypertrophic cartilage cells in chick embryos during endochondral ossification (Harris 1932), I made an accidental observation as a result of which I became interested in the insulin-induced skeletal

* Essay based on work done while Research Fellow in the Department of Orthopaedic Surgery, University of Liverpool (1949–51), for which the Robert Jones Medal and the British Orthopaedic Association Prize for 1951 were awarded.

abnormalities in developing chick embryos. Having confirmed the observation of Harris that the " region of senescent or hypertrophied cartilage cells in the zone of calcification showed the discrete distribution of the particles of glycogen " I proceeded to investigate the effect, if any, of hypoglycaemia—induced in the chick embryos by injections of various doses of insulin into the eggs—on the glycogen granules in the hypertrophic cartilage cells and also on the endochondral ossification in general. I was then aware that Hanan (1925), Vladimirov (1931) and others had induced hypoclycaemia experimentally in chick embryos by injections of insulin into eggs but, to the best of my knowledge, they had not recorded anything about the teratogenic properties of insulin. In the course of my first series of experiments I injected five units of insulin into hens' eggs at various intervals after the beginning of incubation and, to my surprise, noticed that some of the chicks showed radiographic appearances resembling osteogenesis imperfecta in the human. Some of them had developed abnormalities such as spina bifida, partial or complete supression of development of one or more vertebrae, while others showed various deformities in the limbs. Since then a variety of congenital abnormalities have been induced not only with insulin but also with " synthalin," thallium salts, sulphonamide compounds, 3-acetyl-pyridine and cortisone. In this paper I propose to deal only with insulin-induced abnormalities.

REVIEW OF PREVIOUS WORK ON EXPERIMENTAL TERATOGENESIS

An acquaintance with the achievements of the past will not only stimulate independent thinking but also put a check on those tiresome rediscoveries of old facts and observations which only too frequently find their way into modern literature as supposedly new ideas.

NINETEENTH CENTURY BEGINNING OF EXPERIMENTAL TERATOGENESIS

Not only was far greater progress made during the nineteenth century in embryology, foetal physiology and pathology than in any previous century, but also a new type of research was conducted by great pioneers such as Geoffrey Saint-Hilaire, Liharzik, Valentin, Gerlach, Lombardini and Dareste in an attempt to establish on a scientific basis the branch of experimental pathology known as " teratogenesis or the artificial production of malformations or monstrosities." Most of the experiments were carried out on chick embryos during incubation, natural or artificial. Saint-Hilaire (1839) attempted to produce anomalies in the chick by disturbing its development in different ways during the early days of incubation. Various methods were employed such as shaking the eggs, pricking them at various points, keeping them in a vertical position and partly covering them with wax or varnish. These resulted in anomalies like triocephaly, atrophy of the eyes, eventration and spina bifida. Other observers seem to have repeated these experiments with or without modification.

According to Ballantyne (1904), during the fifty years that followed these researches only Camille Dareste stood out supreme in the field of experimental teratogeny. Between 1855 and 1891 he carried out an enormous amount of research and embodied the results of his experiments in a long series of monographs and articles. It was primarily due to him that experimental teratogenesis existed as a special branch of biology. From his numerous experiments conducted by varying the temperature during incubation and careful examination of the monstrous chicks thus produced, Dareste was able to draw important conclusions. He believed that teratogeny was always the consequence of a deviation from normal embryonic development. He regarded almost all malformations of the single embryo as explicable by arrest of development, thus forestalling Stockard's (1907) observations made two decades later. " He differentiated between hemiterata, in which the arrest of development was quite local and was due to a mild teratogenic influence, and the monstrosities proper, in which a stronger teratogenic agent affected a whole region. There were many other interesting questions in teratogenesis which were opened up or cleared up by Dareste but the most important conclusion

he drew from his numerous experiments was that the congenital malformations and monstrosities met with in the chick resembled closely those found in mammalia, especially in the human subject. In this observation Dareste found the germ of the hope that the cause that was active in the chick in teratogenesis might yet be found to apply to the human subject and that human teratology might likewise be elucidated." (Ballantyne 1904).

In 1894 Fére began his series of experiments with hens' eggs. They were divided into three groups. The first group consisted of experiments in which the conditions outside the egg were altered. He repeated many of the experiments of Dareste and others with alterations of temperature, mechanical shaking and varnishing of the egg shell before incubation. He also tried the effect of gases capable of penetrating the shell. Fére placed some eggs in atmospheres containing vapours of turpentine, musk, mercury, phosphorus, ammonia, ether, chloroform, alcohol and tobacco before incubation. The second group consisted of those in which substances in solution were injected into the yolk or albumen of the egg. In this way Fére tested solutions of an incredible variety of substances such as chemicals, microbic toxins, alkaloids, essential oils, various alcohols and other organic substances. " Despite the lack of an intelligent plan the results of Fére's experimental work were very striking. He found, for instance, that there was a direct relation between the teratogenic and toxic powers of poisons " (Needham 1931). Ballantyne (1904) summed up his appreciation of Fére's work in the following words: " Fére has, to my mind, greatly advanced the science of experimental teratogeny by breaking down the dividing wall which was felt to exist in consequence of the particular nature of the supposed exciting causes of monstrosities . . . Another good result followed Fére's work: it gave teratogeny a clinical aspect. If the causes of disease were likewise the causes of monstrosity, then it might be expected that in parents, and especially in the mother, of malformed foetuses, some traces of such morbid causes might be found. The question then arose whether malformed offspring were more common in the alcoholic parents or those suffering from syphilis, tubercle, *infectious fevers* and the like." (My italics.)

EXPERIMENTAL TERATOGENESIS DURING THE PRESENT CENTURY

In view of the large number of experiments that have been conducted during the first half of the present century in different parts of the world, it is proposed to touch upon only the more important among the various investigations, grouping them under certain headings for purposes of convenience instead of following the usual chronological order.

Mechanical injury—According to Needham (1931), teratogenesis by mechanical injury has not been studied so much during this century as in the past, because " the accurate grading of mechanical shocks to living material is a very difficult matter." Scott (1903) investigated the capacity of the eggs of the worm *amphitrite* to develop, without segmenting, into ciliated swimming structures after agitating them mechanically by squirting through a pipette or by other means. Hein (1907) conducted an interesting series of experiments by subjecting the eggs of the trout *salmo fario* to various injuries at different moments in their development. He observed that the period of greatest susceptibility was between thirteenth and seventeenth day of development; for he noticed that both before and after that time the same amount of injury hardly produced the same degree of damage. Hata (1927) repeated Hein's work on two Japanese fishes *onchorynchus mason* and a kind of trout. He employed a " standard vibration treatment " and observed a definite maximum of susceptibility about the sixteenth day of development. Landauer and Bauman (1943) have shown that " rumplessness " can be produced in chickens by mechanical shaking of the eggs. They found that the genetic constitution of the mother played an important part in the extent of the response to mechanical injury. According to them injury to the blastoderm was responsible for " rumplessness."

Thermal injury—Morgan (1904) studied the morphological effect of injury by cold on the eggs of *rana palustria* and came to the conclusion that during post-fertilisation and early cleavage stages the embryos were very susceptible but later their resistance increased. Hein (1911) observed that there were marked differences in susceptibility of trout eggs to temperature changes during their development, and also that the greatest prenatal susceptibility to developmental malformations occurred about the fifteenth day of development or almost exactly at the same time as the susceptibility to mechanical and electrical agents. Higurashi and Nakai (1925) concluded from their experiments with the eggs of a Japanese fish *plecoglossus altivelis* that at first the eggs were very susceptible to teratogenic influences of temperature but became more resistant after the appearance of the " eye-spots " in the embryo.

Teratogenesis by abnormal gas concentrations and anoxia—By far the largest number of researches in ontogenetic susceptibility variations in relation to teratogenesis have been conducted with oxygen lack or carbon dioxide excess, primarily because a given atmosphere is readily prepared, and its effects can be easily observed. Lyon (1902) investigated the effect of placing echinoderm eggs in hydrogen at varying intervals after fertilisation and observed that the embryos were more susceptible during certain phases of development (" critical periods ") than others. Morgan (1905) found that the critical period to anoxia in the development of the frog's egg was after fertilisation and before the first cleavage. If anoxia occurred during this critical interval there was a high incidence of spina bifida, ring embryos and failures of segmentation. Hall (1924) conducted certain experiments on the eggs of the toad *bufo Americanus* with variations in oxygen tension and changes in pH and showed that the first cleavage and gastrulation were again the " critical periods of susceptibility."

Ingalls, Curley and Prindle (1950) submitted pregnant mice to anoxia inside a bell-jar and demonstrated that differences in the degree of anoxia determined not only the frequency of embryonic deaths but also the kind of abnormal offspring of the exposed mice. During an experiment, a vacuum pump continuously exhausted the bell-jar while entrance of the air into the system was restricted by means of an adjustable glove valve. Anencephaly resulted from exposures to " simulated atmospheres " of 25,000 feet and was not found among progeny of animals exposed to 27,000 feet or maintained at " sea level." They have also drawn attention to the " influence of timing of the maternal insult " on the causation of intra-uterine deaths and congenital anomalies. They observed that the specific effects depended on the stage of foetal development and the sites involved when maternal insult occurred. Anencephaly of the foetus was caused by systemic anoxia, obviously with focal involvement of cephalic structure on the eighth day of gestation and cleft-palate resulted in the offspring when the mothers were subjected to anoxic insult on the fourteenth day of gestation. These workers state: " It is reasonable to infer that certain rapidly differentiating cephalic structures are more vulnerable to anoxia on that day than resting cells of fully differentiated tissues." I believe that these experimental observations may have clinical application; and future research may show that during pregnancy maternal anoxia, not necessarily of the rare " anoxic " type but also the commoner " anaemic " and " stagnant " types, may play a significant part in the causation of foetal deaths and congenital defects.

Teratogenesis by x-rays, radium and ultra-violet light—There are a great number of papers on this subject in the literature, even if the discussion is confined to the period of embryonic growth, but many can be disregarded because the experiments were conducted without adequate attention to dosage.

Loeb and Bancroft (1911) used x-rays and radium in treating the common fruit fly *drosophila*. They published a meagre report of their work but they made an important observation that among the radium-irradiated group certain abnormal offspring were noticed in the second generation which bred true, whereas none of the controls showed any of the

abnormalities. In 1922 Mavor observed that irradiation might modify the germplasm and he obtained in *drosophila* a considerable number of abnormal daughters by submitting the mothers to x-rays before mating (Mavor 1922). A certain proportion of these abnormal daughters alone were fertile but they bred true without themselves undergoing any x-ray treatment.

In 1918 Bagg began his classical experiments to investigate the effects of various types of irradiation on animals. He used x-rays, radium emanation and injections of radioactive solutions. He studied the pathological and metabolic changes produced in rats and dogs by injections of radioactive solutions (Bagg 1920); and later the effect of such agents and gamma rays of radium emanation on the functional activity of the ovary and reproduction in the rat (Bagg 1922). Breeding female mice were treated with radioactive solutions of radium emanation at various periods both before and after mating with normal untreated males. In another series of experiments, pregnant rats were irradiated with comparatively heavy doses of gamma-rays. The most constant finding in these animals was the occurrence of characteristic subcutaneous haemorrhagic areas of extravasation in the head region, especially around the eye, and in the feet of the developing embryos irradiated *in utero*. In the case of three litters, similar blood-vascular disturbances were observed in the offspring of mothers irradiated several days (in one case twenty-two days) before mating with a normal male. Marked pathological changes were noted in the brain, which showed evidence of arrest of development, and there were also cataracts and other abnormalities of the eyes in embryos irradiated *in utero* with gamma rays. The prevalence of vascular lesions in the head regions of the embryos, especially in the area surrounding the eye, apparently accounted for the abnormal incidence of eye defects. The abnormalities of the limbs were mainly expressed in various forms of club foot, syndactylism, hypodactylism, congenital amputations and polydactylism. Various combinations of these defects were frequently found in the same limb. Blindness and less severe anatomical defects of one or both eyes, the absence of one or both kindeys and hydronephrosis, usually of one kidney, were the most frequent defects that were associated with abnormalities of the limbs.

Murphy has reviewed the records of 106 women who received therapeutic amounts of pelvic x-radiation during pregnancy. These patients gave birth to seventy-five children at full term, and thirty-eight abnormal children from this group were examined carefully. In twenty-eight, maternal irradiation appeared to be the only factor responsible for their abnormalities. Twenty out of the twenty-eight children suffered from " severe distrubances of the central nervous system." Sixteen had microcephaly. The rarity of microcephaly in the general population (one in 10,000 or more births) suggests that maternal pelvic irradiation was most probably the cause. According to Murphy (1947), maternal pelvic irradiation *before* conception does not influence the growth of the offspring subsequently conceived. He believes that the small amounts of x-radiation employed for diagnostic radiography of the mother's pelvis during pregnancy have no adverse effects on the developing foetus.

Teratogenesis by bacterial toxins and viral infections in experimental animals—Gray and Worthing (1947) produced in chick embryos a localised destruction of the anterior end of the central nervous system with tetanus toxin. They believed that an enzyme inhibitor in the tetanus toxin was probably responsible for the destruction. Blattner and Williamson (1951) have studied the teratogenic action of Newcastle disease virus on developing chick embryos. Virus and control inoculations were made forty-five hours after the beginning of incubation of the eggs. The virus inoculum consisted of allantoic fluid from a twelve-day chick embryo inoculated twenty-four hours previously with Newcastle virus disease. Control inoculum consisted of allantoic fluid from a normal twelve-day embryo. A dose of 0·01 millilitres of inoculum was injected beneath the vitelline membrane over the blastoderm near the edge of the *area pellucida*, the flow from the needle being directed towards the embryo. They observed that the lens and auditory sac showed defective development or were completely

missing in 42 per cent of the 150 infected chick embryos. In the 150 control embryos inoculated with normal allantoic fluid neither defect was found. They have recorded that in their subsequent experiments the specific abnormalities were found in 80 to 90 per cent of the embryos after inoculation with the virus. Preliminary histological studies of the lens defects revealed findings very similar to those observed by Cordes and Barber (1946) and by Swan (1944) in their studies of human foetuses aborted by mothers who had contracted rubella during the first trimestre of pregnancy—namely, retardation in the development of the lens (Cordes and Barber 1946) and necrosis and degeneration of varying degrees in the lens fibres (Swan 1944, Tondury 1951).

Teratogenesis by chemical and hormonal agents—Undoubtedly the most important teratogenic studies during the first two decades of the present century were made by Stockard (1907–21). He carried out most of his experiments in teratogeny with the eggs of the common minnow *fundulus heteroclitus*. He was able to induce a variety of deformities not only by changing the temperature and oxygen content of the environment but also by introducing alcohol and various anaesthetics into the environment. Most of the valuable conclusions which he drew from his long series of experiments have since been confirmed repeatedly by many workers experimenting with different materials.

According to Stockard (1920), the rate of development of an embryo is not uniform throughout the entire process, but periods of rapid progress alternate with those of slow rate or almost quiescence. Such a conception of discontinuity of development led Stockard to the view that there were certain critical points in the development of the embryo at which more damage was caused by an environmental disturbance than at any other time. He also concluded from his experimental observations that the primary action of all teratogenic agents was to inhibit the rate of development. The type of deformity which resulted depended upon the developmental moment at which the interruption occurred. Stockard had located several developmental moments at which rather definite defects of particular organs might be induced. He believed that these were the moments during which the organs were most rapidly proliferating. (It will be seen later how these observations have been confirmed in the case of congenital anomalies induced in chickens by insulin.)

Riddle (1922) was one of the earliest workers to study the suppression of ovulation in adult ring doves by subcutaneous injections of insulin, soon after the successful extraction of the hormone by Banting and Best in 1922. He observed that insulin " blocked ovulation by preventing the ova from beginning their final period of growth and by causing them to be reabsorbed after having entered this stage of growth." In the course of his experiments he showed that the adult birds were highly resistant to the hypoglycaemic effects of insulin, and could survive a dose of the hormone nearly thirty times that which would easily kill a rabbit. Hanan (1925) observed from his own experiments that this resistance to insulin was established early in the embryo. Cassidy, Dworkin and Finney (1926) injected subcutaneously various doses of insulin, ranging from four to 130 units per kilogram body weight, into domestic fowls to determine the effects of severe hypoglycaemia induced by insulin. They noticed that although the extent of the fall of blood sugar after insulin administration in fowls was greater than in mammals, convulsions did not occur and, even after massive doses of insulin (130 units per kilogram), the blood sugar of adult fowls returned to normal autogenously. Vladimirov (1931) studied the effects of injection of water, certain sugar solutions, adrenaline, and insulin into hens' eggs and also the result of filling the air-space in the eggs with carbon dioxide. None of the above-mentioned research workers made any mention of the teratogenic effects of insulin in their published papers.

In 1945, W. Landauer, Professor of Genetics in the University of Connecticut, published a paper entitled " Rumplessness of Chicken Embryos produced by the injection of Insulin and other Chemicals," in which he said: " Incidental to other investigations it was observed that the injection of solutions of certain chemicals into unincubated chicken eggs led to the

appearance of increased numbers of rumpless embryos and chicks." (It is noteworthy that Landauer's observation of the "morphogenetic effects" of insulin was accidental as was my own.) As a geneticist, Landauer was obviously interested in comparing the "morphological appearance of the distal end of the spine in insulin-induced rumplessness" with the sporadically occurring mutations. He was, therefore, content with the naked-eye examination of the chick embryos "which had died between fourteen and eighteen days and between eighteen and twenty-two days of incubation" as well as hatched chicks. Landauer and his associates were not, apparently, concerned with the radiological and histological investigations of the various skeletal abnormalities in embryos of *all* ages and hatched chickens, all of which would, obviously, be of the greatest interest to orthopaedic surgeons interested in the etiology and pathology of congenital malformations. In 1947 Landauer, in a further paper, described the deformities of the beak, eyes and extremities ("micromelia") induced by insulin.

Ancel and Lallemand (1942) who injected over ninety different substances into hens' eggs with a view to inducing malformations succeeded in producing "micromelia" and beak abnormalities in the embryos with only two—namely, eserine sulphate and sulphonamide. In the course of a study of the effects of various agents such as 2-6-diaminopurine (Karnofsky, Patterson and Ridgway 1949), anti-vitamin B6 (Karnofsky, Stock, Ridgway and Patterson 1950), thallium (Karnofsky, Ridgway and Patterson 1950) and cortisone acetate, Karnofsky and his colleagues observed "achondroplasia" in chick embryos treated with thallium and "striking inhibition of growth" with cortisone acetate. Ackermann and Taylor (1948) investigated the results of injection of 3-acetyl-pyridine (structural analogue of nicotinamide, acting, however, as its "antagonist") into hens' eggs. They found that "some of the symptoms associated with the toxicity were undersized deformed legs and a general oedematous-like condition." These effects were reversed by injection of nicotinamide after the administration of 3-acetyl-pyridine. Unfortunately, radiological and histological investigations were not made. (As it was obvious, from the radiological and histological investigations I had made on the very first series of insulin-induced skeletal abnormalities in chick embryos in 1943, that "micromelia" could be due to a generalised developmental disturbance of bone resembling osteogenesis imperfecta in the human, and not necessarily to "achondroplasia" or "chondrodystrophy," as has been suggested by these research workers, I have repeated the experiments with sulphonamides, thallium salts, cortisone and 3-acetyl-pyridine, in order to compare the histological and radiographic appearances of the deformities induced by these substances with those of insulin-induced abnormalities.)

EXPERIMENTAL TERATOGENESIS IN MAMMALS

This is a much more complicated problem because, in the first place, the ovum develops within the uterus; secondly, the placenta is interposed between the foetal and maternal environments; and lastly, experimental treatments cannot be applied to mammals without disturbing the uterus and foetal membranes which, more often than not, leads to abortion. Despite these handicaps, congenital defects have been induced in mammalian embryos by the application of x-rays to the mother during pregnancy as described already (Bagg 1920). Indirect evidence that a perverted metabolism in pregnant women can have serious consequences for the offspring was made available by the valuable contributions of some investigators to the problem of endemic goitre and pellagra (Lavinder and Babcock 1910, Harris 1919). The diversity of factors which, on occasion, can evoke defects in the offspring of man and other mammals have been carefully examined in two excellent reviews by Warkany (1945, 1947).

Gillman and his associates (1948) have induced in rats congenital abnormalities such as hydrocephalus, spina bifida, eye and ear defects, and malformations of the tail by subcutaneous injections of trypan blue to the mothers during gestation. The total number of 100 female rats they used in their experiments was composed of two series. Every rat in both series

received an injection of one millilitre of 1 per cent aqueous solution of trypan blue during gestation but the rats in the second series had received, in addition, a variable number of injections before conception. In the series of rats receiving injection treatment during gestation (on the eighth or ninth day after conception) only 3 per cent of the offspring showed congenital malformations. In the second series of rats, which received injections before conception and during gestation, the incidence of abnormal offspring was much higher, ranging between 65 and 80 per cent.

Corda (1932) observed that pregnant rabbits injected with insulin aborted or produced young ones that were undersized. Lichtenstein, Guest and Warkany (1951) found that protamine zinc insulin, when administered in suitable doses to pregnant albino rats throughout the period of gestation, had significant effects on foetal development. The average weight of the foetuses of the insulin-treated rats was lower than that of the controls and the number in each litter was less owing to foetal deaths and resorption. They also noticed certain skeletal abnormalities such as a " decreased number or complete absence of ossification centres in the sternum." In some of the foetuses of the insulin-treated rats the long bones, such as the femur and the humerus, seemed " short in relation to the body size " and showed irregularities in ossification at their ends. Some of these foetuses showed " wavy ribs." (It is indeed gratifying that some of my observations on insulin-treated skeletal abnormalities in chickens have been paralleled in mammals.)

TERATOGENESIS BY MATERNAL NUTRITIONAL DEFICIENCIES

In recent years a number of publications have appeared, indicating that congenital malformations in the offspring of animals may be due to a faulty maternal diet. Ivanovsky (1923), in a report on the physical modification of the population of Russia under famine, remarked: " The number of children either prematurely born or stillborn, monsters, and children with different anomalies considerably increased during the famine." According to Murphy (1947) the diets of mothers who gave birth to children with congenital deformities were " significantly lacking in adequate amounts of calcium, phosphorus, iron, and vitamins B, C and D." Iodine deficiency during pregnancy results in the birth of defective offspring or foetal deaths. Cretins are usually born of goitrous mothers in endemic mountainous areas. Manifestations of prenatal iodine deficiency have also been described in horses, cattle, pigs and lambs. The thyroid of the offspring is enlarged, hyperaemic and poor in iodide. According to Smith (1917), one million pigs were lost in the United States in 1917 because of prenatal iodine deficiency. Such pigs were born hairless, and their skin was myxoedematous. Smith showed that these defects could be prevented by the administration of potassium iodide or thyroid of sheep.

Hale (1935) reported that sows fed on rations deficient in vitamin A gave birth to piglets with blindness or without eye-balls. In addition, microphthalmos, misplaced kidneys, cleft palate, hare-lip and other abnormalities were noticed. Hale showed that genetic factors could be ruled out as the cause of these malformations. Moore, Huffman and Duncan (1935) observed that calves born to vitamin-A-deficient cows were blind. Andersen (1941) reported a high incidence of congenital diaphragmatic herniae in the offspring of rats fed on a vitamin-A-deficient diet. Ross and his co-workers (1944) noticed in swine congenital malformations of nutritional origin such as syndactylism, " talipes," kinked tail and ocular defects.

Warkany and his associates (1948) have shown that a syndrome of multiple congenital anomalies can be induced in the progeny of rats reared and bred on a vitamin-A-deficient diet. They were as follows: ocular anomalies such as retrolenticular membrane replacing the vitreous, coloboma and folding of the retina, rudimentary development of the lungs and pleural cavities, cardiac septal defects, anomalies of the aortic arch, diaphragmatic hernia, tracheo-oesophageal fistula, and a variety of congenital defects in the genito-urinary system.

Warkany and co-workers (1940, 1942, 1943) found that female rats reared and bred on a

diet deficient in riboflavin gave birth to offspring a third of which had congenital skeletal abnormalities. The malformations consisted of shortening of the mandible, tibia, fibula, radius and ulna, cleft palate and fusion of the ribs. According to Silberberg and his colleagues (1948), deficiency of vitamin B-complex in growing rats causes retardation and finally cessation of growth of cartilage and bone, associated with " serous atrophy " of the bone marrow. They found that after refeeding with a stock diet containing an adequate amount of vitamin B-complex, skeletal growth was resumed at an intensified rate, resulting in early restoration of the normal condition. Byerly and his associates (1935) obtained short-legged embryos from eggs laid by chickens reared and bred on a deficient diet whose effects were reversed by wheatgerm, liver and whey. Romanoff and Bauernfeind (1942) demonstrated in chickens that riboflavin deficiency gave rise to " micromelia " and beak deformities in the progeny. Couch and his co-workers (1948) obtained similar abnormalities with biotin deficiency. Lyons and Inkso (1937) observed that a diet deficient in manganese also gave rise to " micromelia " and beak deformities in the offspring.

This new knowledge in the field of nutrition deserves special attention, since it demonstrates clearly the effect of vitamin deficiencies upon the earliest processes of growth and differentiation.

EPIDEMIOLOGICAL IMPLICATIONS OF DEVELOPMENTAL ARRESTS AND OTHER RELEVANT OBSERVATIONS

Rubella—Epidemiological events in the past decade have demonstrated that the broad principles that govern the disturbances of growth and differentiation in lower animals can be applied, with suitable modifications, to human developmental arrests and malformations. From time to time the possibility that maternal intercurrent infections may cause congenital defects in the foetus has been discussed and the role of syphilis has long been recognised. However, it was not until Gregg (1941) drew attention to the association of developmental anomalies in the offspring such as cataract and cardiac septal defects with maternal rubella in the early months of pregnancy, that it became an established fact. A masterly review by Swan (1949) has surveyed the evidence against rubella upon more than 558 recorded cases in which there appeared to be a definite relationship between maternal intercurrent infection and the development of congenital malformations. Swan concluded from his survey that a woman who had contracted rubella during the first four months of pregnancy had a three to one chance of giving birth to a congenitally deformed infant.

Although there can be little doubt from the formidable array of statistics so far accumulated that maternal rubella is in some way causally related to congenital abnormalities in infants, it is still not certain whether these statistics reflect the true situation. According to Fox *et al.* (1948) rubella " increases the risk of congenital anomalies from the usual figure of 0·9 per cent to about 15 per cent." These observers have also made a report on the possible role of measles, mumps and chicken-pox in the causation of congenital malformations. Parsons (1946) suggested that in mammals " the embryonic cells are more susceptible to virus infections than adult tissues; more severe changes, therefore, should be seen in the foetus and these should be especially marked at the period of greatest embryonic activity, viz., the early weeks of pregnancy." From his survey of the Australian and American literature, Wesselhoeft (1947) compiled a list of major malformations seen in infants born to mothers contracting rubella at some stage during pregnancy. The congenital anomalies included eye defects, deafness, heart lesions, microcephaly, dental defects, mental retardation and pyloric stenosis. To this list may be added hydrocephalus (Fox and Bortin 1946), congenital obliteration of the bile ducts, mongolism, imperforate anus, myelocele, " bilateral talipes," spina bifida occulta, spastic diplegia, cleft palate, unilateral Horner's syndrome and hemiparesis, umbilical hernia, strabismus, cryptorchidism, buphthalmos, hypospadias and genu valgum (Swan *et al.* 1943, 1946). Moreover, stillbirths, premature births and abortions were commoner (Goar and Potts 1946).

Time relationship between the maternal rubella and the type of malformation—Aycock and Ingalls (1946) tried to correlate the month of infection during pregnancy with the occurrence of a particular congenital malformation in the infant after taking into account all the recorded findings of various authors, and stated: "The average period of pregnancy when rubella occurred was as follows: for cataract, six weeks; for deafness, nine weeks; for cardiac anomalies, five to ten weeks; for deformed teeth, six to nine weeks." Swan and Tostevin (1946) have made the following observations of the time relationship: "The obvious conclusion, however, is that in man the primordia of the various organs have relatively long so-called 'critical moments.' Our experience suggests that in general the 'critical moment' of the optic cup is the first three months of pregnancy, and that of the cochlear anlage is the second, third and fourth months. We believe, moreover, that averages such as we have drawn above may indicate the period of greatest susceptibility of the anlage of a particular organ, for example, lens or cochlea to the virus of rubella."

According to Tondury (1951), who reviewed Bourquin's statistics (1948) based on 146 cases of congenital cataract due to maternal rubella, the maximal incidence of this developmental anomaly was observed when the mother contracted the infection during the fourth and fifth weeks of pregnancy; after this period its incidence became less frequent up to the twelfth week, when it disappeared almost entirely. It may be recalled that at the end of the fourth week or the beginning of the fifth week (twenty-eighth to thirtieth day) the crystalline plate appears in the epidermis which covers the ocular cuticle. Between the thirtieth and thirty-fifth days, the crystalline vesicle becomes isolated and at the end of the sixth week (fortieth to forty-second day) the first crystalline fibres begin to differentiate. The "critical period" for the formation of a congenital cataract would therefore appear to coincide with the processes of differentiation of the embryonic crystalline lens.

Tondury (1951) had an opportunity to examine the malformed lenses of five aborted foetuses. The maternal intercurrent rubella infection was during the first trimester of pregnancy in all the five. He noticed in a 21-millimetre embryo (the youngest in his series) that "the disposition of the lens was normal, but the fibres during differentiation showed a vacuolar deformation." An embryo of 64 millimetres had a central degeneration of the lens and, in addition, it could be seen that this destructive process had reached the fibres of the lens which were formed secondarily. He observed the same type of degeneration of the lens fibres in a foetus of 32 centimetres, as well as in a stillborn infant. (It is significant that Tondury observed evidences of degeneration in the lens fibres which had apparently developed normally up to a certain stage in all the five foetuses. Analogous degenerative changes are induced by insulin in cartilage models which have developed normally up to a particular stage, depending on the time of injection of the hormone, as will be seen later.)

Mongolism—By epidemiological methods an association has been observed between mongolism in the offspring and a variety of maternal uterine or systemic diseases present or operating between the seventh and ninth weeks of foetal life (Ingalls 1947). This observation has been confirmed by Lowe's (1949) studies of the eyes of fifty-two mongoloid children. Lenticular opacities were among the earliest consistent ocular abnormalities. Because of their position within the nuclear part of the lens, Lowe came to the conclusion that their genesis lay in relation to an abnormal capsulo-pupillary vessel during early foetal life, "a critical stage of development corresponding to a foetal length of 35 millimetres or a foetal age of 8·5 weeks." According to Ingalls (1947), "diverse causative agents are involved in the pathogenesis of mongolism and foetal anoxia may be an important pathogenic mechanism."

Bleyer (1938) plotted the ages of 2,822 mothers who gave birth to mongoloid infants against the ages of more than two million mothers in the United States who gave birth to normal infants during 1934. He observed that a significantly high percentage of the mothers who gave birth to mongoloid offspring were about forty years old. Thus he was able to show

a definite association between mongolism and relatively advanced age of the mother. Other factors which have been identified in the causation of mongolism are: gestational haemorrhage; mechanical disorders of the uterus; and intercurrent infection such as rubella, influenza, mumps and purulent otitis media (Ingalls and Gordon 1947).

Encephalo-ophthalmic dysplasia—Epidemiological methods applied to encephalo-ophthalmic dysplasia (retrolental fibroplasia) have confirmed Terry's (1943) observation that it is related to prematurity and multiple pregnancy. Thirteen out of twenty-six children whose birth weights were recorded weighed under three pounds at birth. It was found that eleven out of seventy-seven mothers were multiparae, eight had intercurrent infections, three had toxaemia of pregnancy, two had placenta praevia, and eighteen had suffered from gestational haemorrhage (Ingalls and Gordon 1947). The association between the malformations and the maternal condition was indicated by the frequency of toxaemia of pregnancy, multiple births, and placenta praevia, as compared with chance expectancy, and also by the grouping of haemorrhages and intercurrent infections during or shortly after the second trimester of pregnancy.

Congenital oesophageal atresia with tracheo-oesophageal fistula—Ingalls and Prindle (1949) reviewed the records of 107 infants with congenital atresia of the oesophagus and it is noteworthy that they found no case in this series in which the defect had appeared in successive generations or in other members of the family. One hundred and two of these infants had associated tracheo-oesophageal fistulae. They also observed other co-existing congenital anomalies in the cardiovascular, gastro-intestinal, respiratory and skeletal systems. On the basis of the morphology of the tracheo-oesophageal defect, and that of the associated arrests, they postulated that the syndrome is acquired during early foetal life at about the fifth or sixth week of intra-uterine development. In the course of a study of the possible maternal factors responsible for the congenital anomalies they observed that there were four twin-pregnancies, six mothers had antepartum haemorrhages (five in the first or second months of pregnancy) and six had suffered from acute infections or metabolic disturbances in the first trimester of pregnancy (Ingalls and Prindle 1949). On the basis of these and other relevant observations they put forward a hypothesis that "oesophageal atresia, tracheo-oesophageal fistula and certain other commonly associated defects represent departures from normal development about the fifth or sixth week of embryonic life, caused by agents acting through the mother and placenta."

Toxoplasmosis—Since toxoplasma infection in man was first recorded by Wolf, Cowen and Paige (1939a, 1939b) it has become recognised in many countries, but the frequency of the infection is still unknown. The protozoon causes a low-grade inflammation in the foetal tissues, particularly in the nervous system. Its clinical manifestations in the early months after birth are numerous, the most frequent being meningo-encephalitis, microphthalmos, bilateral chorio-retinitis in the central area of the fundus, and hydrocephalus or microcephalus (Capon 1950). Intracranial calcification may be observed radiologically and the child is often retarded mentally and liable to have convulsions. Few opportunities have arisen in Britain for studying a series of cases for less than a dozen cases had been reported up till the middle of 1950 (Lancet, 1950, **ii**, 578). Most of the available information on the subject has come from Sabin and Feldman (1949) in the United States. Only future research can prove whether or not congenital toxoplasmosis is a common cause of developmental abnormalities. However, it has been demonstrated clearly that the infection can pass through the "placental barrier" in the same way as rubella and cause a low-grade inflammation in the foetal tissues. This, in itself, is a significant observation.

Congenital malaria—Another protozoal infection, malaria, may perhaps be a cause of congenital defects among children of non-immune mothers who move into endemic areas. Very few genuine cases have, however, been reported in recent literature, and even these have not been investigated thoroughly. This problem should be explored completely because it

has been shown that the immunity to malaria varies a great deal even among the local inhabitants in tropical countries, not to speak of non-immune mothers moving into highly malarial areas.

Maternal iso-immunisation—Much attention has been given in recent years to the subject of maternal iso-immunisation by antigens present in the blood of the foetus (inherited from the father) though lacking in the mother's blood (Mollison, Mourant and Race 1948, Cappell 1948, Allott and Holman 1949). Maternal Rh iso-immunisation may interfere with normal foetal development and result in extensive abnormalities of the central nervous system. According to Yannet (1950) the most common clinical picture includes the following features: severe mental deficiency, asymmetric hypertonicity and weakness of the extremities, neck and back, and choreo-athetosis. Yannet states: "In practically all cases it should be possible to obtain a neonatal history compatible with *erythroblastosis foetalis* and an Rh set-up in mother and child consistent with this diagnosis."

Yannet and Lieberman (1948) have reported an ABO mother-child incompatibility and suggested the possibility that certain cases of congenital mental deficiency may be the result of maternal AB iso-immunisation. According to them, the "infrequency of a significant history of *erythroblastosis foetalis* in these cases, the normal incidence of the first-born, and complete absence of specific neurological disorder suggest that the pathogenesis in these cases may be different from that present in Rh iso-immunisation."

FOETAL ABNORMALITIES ASSOCIATED WITH MATERNAL ENDOCRINE DISORDERS

Diabetes mellitus—In recent years the role of maternal diabetes in teratogenesis has been studied. The foetal and neonatal mortality rate of infants of diabetic mothers is abnormally high. In the pre-insulin era, diabetic women often had amenorrhoea and were frequently sterile. White (1940) showed that with the introduction of insulin the fertility of diabetics improved and the maternal mortality dropped to levels comparable with non-diabetic women. However, the early and late foetal deaths fell only from 44 to 38 per cent.

In diabetes mellitus there is very definitely a higher incidence of congenital abnormalities than normally. Oakley and Peel (1949) reviewed 142 cases examined at King's College Hospital, London, and found that in addition to minor blemishes such as skin naevi, which were particularly common among these cases, there were more serious abnormalities—an incidence of 6·3 per cent as compared with a general incidence of 0·94 per cent in 4,829 deliveries in normal mothers. They noted the following congenital anomalies in their series: internal hydrocephalus, congenital heart defects, hemi-vertebrae, imperforate anus, congenital dislocation of the hip, cleft palate, renal tract deformities, absence of sacrum and coccyx, and talipes equino-varus.

Joslin and co-workers (1940) observed that four infants out of fifty-one in their series were malformed: the first had a club foot, claw hand, webbed toes and missing fingers; the second showed a congenital heart lesion; the third had congenital dislocation of both hip joints; and the left hand of the fourth infant had no fingers.

Miller (1946) found that in nineteen consecutive necropsies on infants born to diabetic mothers seven had one or more malformations which included: anecephaly; bicuspid pulmonary valve; cor biventriculare, hypoplasia of the aorta; double left ureter, hydro-ureter, hydronephrosis; persistent pupillary membrane; agenesis of the urinary bladder and kidneys, malformation of ureters; harelip, agenesis of the gall-bladder, bicornuate uterus, septate vagina, hypoplasia of the right humerus and femur, agenesis of the left femur and fibula, syndactylism, and agenesis of the thoracic vertebrae. Miller states that these congenital malformations were reviewed by G. W. Corner, Director of Carnegie Institute of Embryology. Corner concluded from his examination that in all instances the malformations were present before the end of the third month of intra-uterine life. The actual mechanism of causation of the various congenital anomalies, which include orthopaedic deformities, is not known at

present. I believe that chorionic gonadotropin may play a part in their causation, and future research on these lines may be rewarding. It is known that chorionic gonadotropin begins to rise on the thirty-fifth day after the last menstrual period and reaches its peak between the fiftieth and seventy-fifth day of pregnancy. This period corresponds significantly with the " critical periods " of the various organs and tissues showing the above-mentioned congenital anomalies. Corner's belief that all the malformations originated before the end of three months supports this hypothesis.

This hormonal conception of the problem of pregnancy with diabetes mellitus is the natural outcome of our knowledge that many abnormal pregnancies have an abnormal endocrine background. The first suggestion of a possible hormone imbalance in diabetic pregnancies was made in 1933 by Murphy who reported that the chorionic gonadotropin excretion of two diabetic women exceeded the normal. Excess of chorionic gonadotropin, or deficiency of oestrin and progestin after the fifth month of pregnancy, may be followed by toxaemia and premature deliveries resulting in high foetal mortality (Joslin *et al.* 1940). Substitutional oestrin and progestin therapy has controlled the rise of serum gonadodropin and as a result late foetal mortality has fallen from 32 per cent to 6 per cent or nearly to the level of non-diabetic pregnancies—3·4 per cent (Joslin *et al.* 1940). However, treatment given in the third trimester of pregnancy could hardly be expected to influence the incidence of congenital malformations since they are most probably determined in the first trimester. (On the basis of the hypothesis put forward above, I would like to suggest that the substitutional oestrin and progestin therapy should be started in diabetic women almost immediately after any missed period, instead of waiting till the fifth month of pregnancy.)

Recent studies have shown that striking changes often occur in many of the tissues of children born to diabetic mothers. In addition to increased body weight and hyperplasia of the islets of Langerhans, both of which have been recognised for many years, it has been shown that these infants sometimes have, at birth, cardiac hypertrophy, extramedullary erythropoiesis (Miller and Wilson 1943), adrenal hyperplasia (Miller *et al.* 1944), increase in the eosinophil cells of the anterior hypophysis (Bauer and Royster 1937), and hyperplasia of the genital organs in the female (Smyth and Olney 1938). In the course of their studies of infants born to diabetic mothers Miller and Wilson observed that many of these changes were present in infants born to mothers who did not show any evidence of diabetes during pregnancy, but developed it at varying periods after delivery (Miller 1945). The birth weight of such infants is also greater than the average normal and the total foetal mortality rate in such pregnancies is greater, as in the case of infants of mothers who actually suffer from diabetes during pregnancy. These findings lead us to conclude that, even in the pre-diabetic phase, there is an endocrine imbalance in these women which may interfere with the normal development of the foetus *in utero*.

MATERIAL AND METHODS

My experiments were conducted with eggs from brown leghorn and light Sussex flocks which were known to be free from genetic abnormalities. The riboflavin and manganese contents of the eggs were found to be adequate from routine testing at fairly frequent intervals.

I have used a simple apparatus (Fig. 1) not only for testing the fertility of an egg before injection, but also for transilluminating it while drilling a hole into the shell and injecting into the yolk. In this way, I have avoided injuring the embryo and its chorionic blood vessels, which very often causes the death of the embryo. A fine dental drill held in a small chuck has been used to make a hole in the egg-shell manually in order to avoid any possible trauma to the embryo by the mechanical vibrations of an electric drill. A tuberculin syringe fitted with the finest hypodermic needle 2 centimetres long has been found most suitable for making the injection into the yolk.

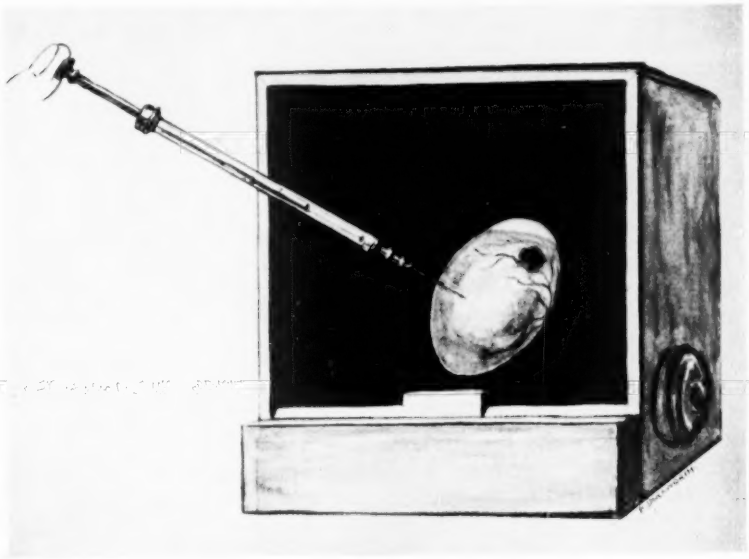


FIG. 1

Apparatus for transilluminating the egg during injection to avoid injury to the embryo and the chorionic blood vessels.

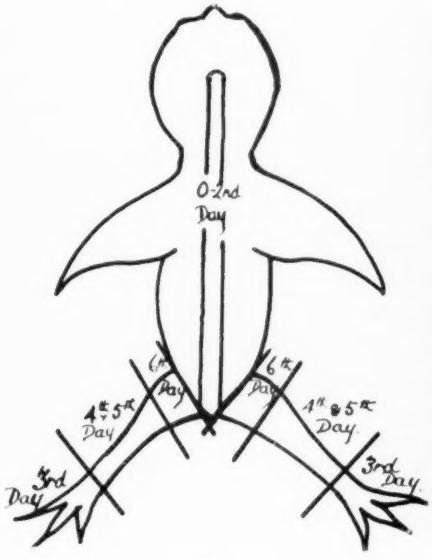


FIG. 2

Site of deformity induced by insulin related to time of injection into the egg after incubation.

FIG. 3

Normal twenty-days-old embryo extracted from the shell before hatching.

I have employed solutions of crystalline insulin made up to a strength of 40 units in each millilitre. The doses ranged between 0·05 and 6 units, and the injections were made at different intervals after the beginning of incubation. Calculated on the basis of the human dose, these doses may be considered distinctly excessive. However, as has already been mentioned, Riddle (1923) and others have shown that birds are highly resistant to insulin and can survive a dose thirty times as strong as that which would kill a rabbit. Whenever the volume of the solution injected has exceeded 0·05 millilitres, an additional hole has been drilled into the egg-shell in the region of the air sac in order to prevent undue increase of pressure inside the egg. I should perhaps make it clear, at this stage, that only one injection of insulin is made into the egg and no more is given either during the remaining period of incubation or after hatching.

After injection, the needle is carefully removed and the hole in the egg-shell is sealed and the egg returned to the incubator. With the same technique, control injections, such as physiological saline, and substances which are known to play a part in ossification, such as calciferol, parathormone and radioactive phosphorus, have been injected into eggs incubated in the same incubator. Care has been taken to eliminate, as far as possible, known teratogenic factors such as fluctuations of temperature and humidity during incubation. Physical conditions of incubation may be accepted as satisfactory since hatches averaged 85 per cent of fertile " uninjected " eggs. In all experiments equal numbers of control eggs were placed in the same incubator in which eggs treated with insulin were incubated. Embryos have been removed at varying intervals after injection for histological and other investigations. Chicks that survived fourteen days after the beginning of incubation and those that hatched out alive either by themselves or with help, as in the case of deformed ones, have been radiographed. All the chicks, insulin-treated as well as controls, have been fed on a nutritious diet containing adequate amounts of vitamins and essential minerals such as calcium, phosphorus and manganese, and reared under equal conditions in every way. It should be noted that nearly all the chicks treated with insulin are more " delicate " than the controls so that they have to be reared with special care.

It has been observed that a certain percentage of the insulin-treated fowls, both male and female, are sterile, but the remaining fertile males and females showing insulin-induced abnormalities such as "osteogenesis imperfecta" and "club foot" were mated and the eggs resulting from these matings have been incubated *without any treatment whatsoever*. Some of these eggs have been opened and embryos removed at various stages for histological, radiological and other investigations. The hatched chicks were reared on the same nutritious diet as the rest for further breeding, if possible, through successive generations. (Though some of the insulin-induced abnormalities seem to have been passed on to their offspring by the insulin-deformed parents (Figs. 41 to 49), I do not propose to discuss this aspect of the problem in the essay, as it is essential to ascertain whether the abnormalities are transmitted to the descendants of the third and subsequent generations, as is being done now, before any conclusions are drawn from these experiments.)

ESTIMATION OF BLOOD SUGAR IN INSULIN-TREATED AND CONTROL CHICK EMBRYOS

Blood sugar estimations were made by the Hagedorn-Jansen method (modified) at different intervals after the injection of insulin to study the degree and course of hypoglycaemia. Similar estimations were conducted on appropriate controls for comparison. A volume of 0·02 millilitres of blood was collected with the help of a haemoglobinometer pipette from the vitelline or the allantoic veins, depending on the stage of growth of the embryos. In the case of the early ones, six or seven days old, pooling of blood from two embryos which had been treated with the same dose of insulin had to be resorted to.

HISTOCHEMICAL METHODS

I have employed Lison's histochemical technique (Lison 1935) for staining the mucopolysaccharide complexes (chondroitin-sulphuric acid complexes) in cartilage with a basic

metachromatic aniline dye such as toluidine blue. Lison has presented evidence to show that the metachromatic staining reaction is specific for the mucopolysaccharide complexes, the affinity of which for the dye is so great that even in very high dilutions (1 in 250,000) the cartilage containing the mucopolysaccharides is stained deep purple red (metachromatic) while the other tissues stain blue (orthochromatic). By using this technique I have observed that the cartilaginous skeleton in the insulin-treated embryos exhibits less affinity for the dye than the controls and also shows degenerative changes and deformities (Figs. 31 to 33).

In addition to toluidine blue stain I have employed another histochemical reaction for polysaccharides. This is the periodic acid-leucofuchsin technique, first introduced by McManus (1946) and later improved by Hotchkiss (1948). It is regarded by most workers in the field as a highly specific test for polysaccharides such as chondroitin-sulphuric acid complexes and glycogen. It is easy to distinguish between the two polysaccharides because the glycogen granules are within the cartilage cells whereas the mucopolysaccharide is stained in the intercellular matrix. Further, only the glycogen particles disappear after treatment with saliva or diastase. According to Rubin and Howard (1950), by making use of both these histochemical methods, one can demonstrate the localisation of both the polysaccharides with considerable assurance.

TISSUE CULTURE EXPERIMENTS

The main aim of this aspect of my research was to investigate the possible mechanism involved in the induction of developmental abnormalities by insulin, by growing limb buds and cartilaginous models (of bones developed from cartilage such as the femur and the tibia) *in vitro* and *in vivo*, in the presence of varying concentrations of insulin. It is, however, not proposed to include details of these investigations in this essay.

OBSERVATIONS

Broadly speaking, insulin seems to affect primarily the part of the body or tissue that is in the most active stage of growth or differentiation at the time of injection. Table I and Figure 2 indicate the type of deformity that has been induced by insulin in relation to the time of injection after the starting of incubation of the egg. Figure 3 shows a normal twenty-days-old chick embryo; examples of the abnormalities that have been induced (mostly by insulin, a few by other agents) are shown in Figures 4 to 50.

TABLE I

INSULIN-INDUCED SKELETAL ABNORMALITIES

Day of injection after starting of incubation	Part of the body primarily affected by insulin
First and second days	Vertebral column
Third day	Feet
Fourth and fifth days	Limbs; beak
Sixth day	Hip (congenital dislocation)
Third to sixth days (high doses of insulin —3 to 6 units)	Generalised developmental disturbances of bone as seen in osteogenesis imperfecta, achondroplasia, chondro-osteo-dystrophy, etc.

Relationship between the dose of insulin and the incidence and severity of the deformity—Within the range of 0·05 to 6 units of insulin that I have injected, the incidence and severity of the deformities seem to increase with the dose of the hormone (Tables II and III). These should be compared with Table IV, which shows the incidence of abnormal foetuses in untreated groups.

TABLE II

RELATIONSHIP BETWEEN THE DOSE OF INSULIN AND THE INCIDENCE OF ALL TYPES OF DEFORMITIES OF THE VERTEBRAL COLUMN

(The injection of insulin into the yolk was made twenty-four hours after the beginning of incubation)

Dose of insulin	Percentage of all types of deformities of the vertebral column
1 unit	18·1
1·5 units	20·6
2·5 units	25·2
5 units	31·0
6 units	36·3
Controls injected with the same volume of saline	1·3

TABLE III

RELATIONSHIP BETWEEN THE DOSE OF INSULIN AND THE INCIDENCE OF ALL TYPES OF DEFORMITIES OF THE LIMBS

(The injection of insulin was made 120 hours after the beginning of incubation)

Dose of insulin	Percentage of all types of deformities of the limbs
1 unit	26·3
1·5 units	32·2
2·5 units	46·0
5 units	85·0
6 units	89·6
Controls injected with the same volume of saline	2·2

TABLE IV

TABLE DRAWN UP BY HUE AND GREENWOOD (1929) OF THE SPONTANEOUSLY OCCURRING MONSTERS AND CONGENITAL DEFECTS IN A SURVEY OF 12,000 CHICK INCUBATIONS

(For comparison with insulin-induced deformities as given in Tables II and III)

	Percentage of total chicks	Percentage of total anomalies
Hypetencephaly (absence of eye-cups, cranial roof, etc.)	1·52	41
Exencephaly (failure of skull formation—brain extrudes through meninges)	0·84	23
Microphthalmia and anophthalmia (eye-cups abnormally small or entirely absent)	0·81	22
Exencephaly and microphthalmia	0·25	7
Miscellaneous (including ectopic viscera, malformed limbs, otocephaly, complete absence of the head and various duplicities)	0·25	7

FIG. 4

FIG. 5

Spina bifida in an embryo treated with insulin twenty-four hours after incubation and removed from the shell alive on the twentieth day of incubation. Figure 4—Posterior view. Figure 5—Lateral view. Note the anophthalmos and short upper beak.

FIG. 6

FIG. 7

Figure 6—Scoliosis in an insulin-treated chick four months old. When hatched the chick appeared to be normal. Figure 7—Photograph, taken from above, of the thoracic cage removed from a chicken eight months old with scoliosis, to show the secondary deformities produced by rotation of the vertebrae.

FIG. 8

FIG. 9

Figure 8.—"Lobster" claw in a twenty-days-old chick embryo injected with two units of insulin on the third day of incubation. Note the "parrot" beak. Figure 9.—Club feet associated with arthrogryposis in a twenty-days-old embryo treated with 0·05 millilitres of a 10 per cent solution of a sulphonamide compound (Soluseptasine) on the fourth day of incubation.

FIG. 10

FIG. 11

Figure 10.—Club feet in a twenty-days-old embryo. Three units of insulin had been injected on the third day of incubation. Figure 11.—Club feet associated with arthrogryposis in a twenty-days-old embryo. Compare with Figure 10. (Three units of insulin on fifth day.)

FIG. 12

Club feet in a chicken eight months old. Note the adventitial bursae in the feet.

FIG. 13

Radiograph of the club feet of the same chicken seen in Figure 12. Note the soft-tissue shadow cast by the adventitial bursa of the left foot.

FIG. 14

FIG. 15

Figure 14.—Radiograph of a three-weeks-old insulin-treated chick with bilateral dislocation of the knees. Note the bilateral angulations of the tibiae ("tibial kyphosis") at the junctions of the middle and lower thirds—the level at which pseudarthrosis usually occurs. Figure 15.—Congenital bowing of the tibia in a six-months-old insulin-treated chicken. Bowing affects *upper* third, whereas in "tibial kyphosis" the angulation is at the junction of the middle and lower thirds, as in the corresponding human deformities.

FIG. 16

Sagittal section of a tibia from a twenty-days-old embryo showing pseudarthrosis. Note that the whole tibia is abnormal, with poor subperiosteal bone formation.

FIG. 17

Congenital dislocation of the left hip in a four-weeks-old chick (egg treated with insulin on the sixth day of incubation). Note the lateral rotation of the left limb due to the dislocation being anterior.

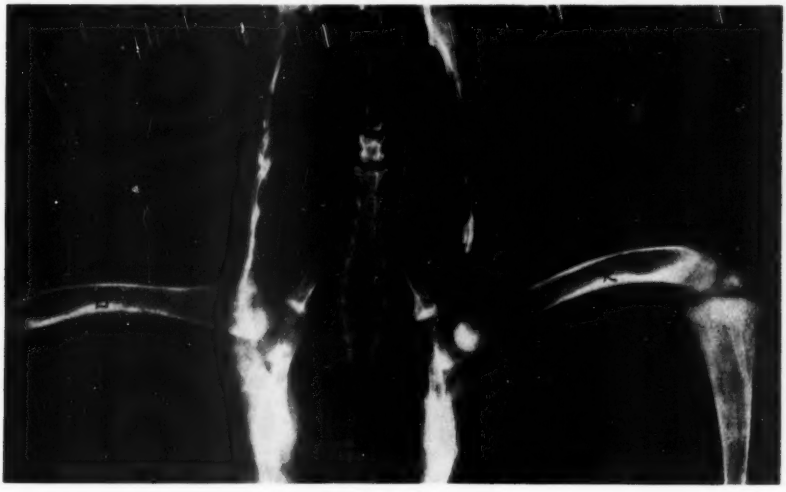


FIG. 18

Radiograph of the chick shown in Figure 17 (posterior-anterior view).

FIG. 19

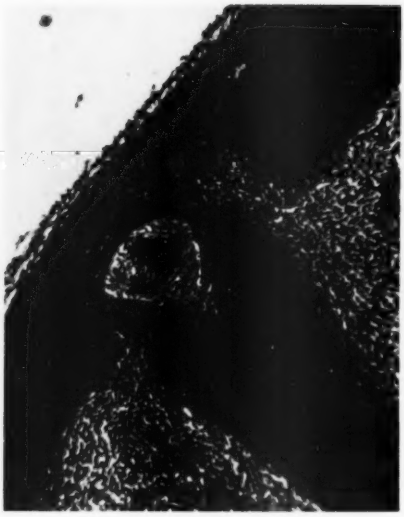


FIG. 20

Figure 19—Sagittal section (× 18) of the left hind limb of a seven-days-old insulin-treated embryo showing areas of degeneration in the upper ends of the femur and tibia. These may result in the alteration of the hereditary forms of epiphyses which may be followed by dislocations, as suggested by Harris (1933). Similar changes have been noticed in the acetabulum. Figure 20—Photomicrograph (× 100) to show the degenerative changes in the upper end of the femur.

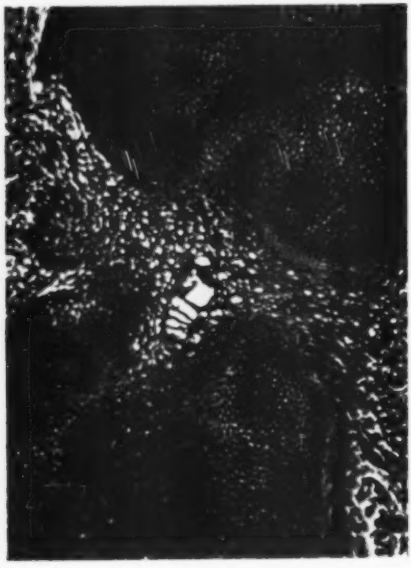


FIG. 21

FIG. 22

Figure 21—Photomicrograph (× 100) of a sagittal section through the knee joint of an insulin-treated twelve-days-old embryo showing degenerative changes in the articular ends of the femur and tibia. The joint space, which should be clear and well defined at this stage, is filled with degenerated cartilage cells. Figure 22—Photomicrograph (× 100) of a sagittal section through a normal knee joint of a twelve-days-old embryo.

FIG. 23

FIG. 24

Figure 23—Twenty-days-old embryo showing insulin-induced " micromelia " due to a generalised developmental disturbance of bone resembling osteogenesis imperfecta. Compare with Figure 3, which is on the same scale. Note the " parrot " beak. Figure 24—Radiograph of a twenty-days-old chick embryo treated with 5 units of insulin on the fifth day of incubation, showing generalised developmental disturbance of bone resembling the pre-natal type of osteogenesis imperfecta, with defective ossification, typical deformities and pathological fractures.

FIG. 25

Radiograph of a twenty-days-old chick embryo with insulin-induced osteogenesis imperfecta (pre-natal type). The appearance of the skull is due to an artefact.

FIG. 26

Sagittal section (× 8) of the tibia of a twenty-days-old chick embryo treated with 5 units of insulin on the fifth day, showing osteogenesis imperfecta (pre-natal type) with pathological fracture and deformity of the tibia.

FIG. 27

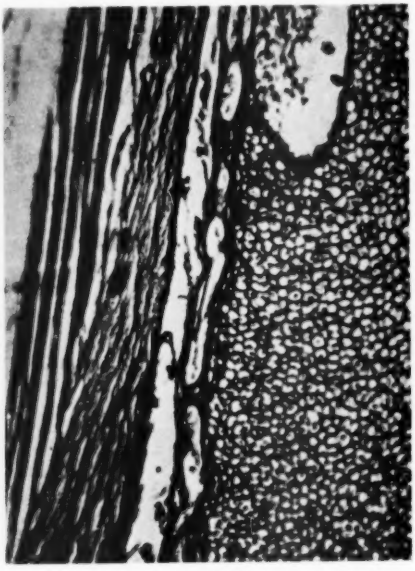


FIG. 28

Figure 27.—Photomicrograph (× 100) of a longitudinal section of the tibia in a twenty-days-old normal chick embryo to show the amount of subperiosteal bone formed and the appearance of the marrow cavity. Figure 28.—Photomicrograph (× 100) of a comparable section taken from the tibia of insulin-treated embryo of the same age. Note the lack of subperiosteal ossification and the thickening of the periosteum, as seen in human osteogenesis imperfecta.

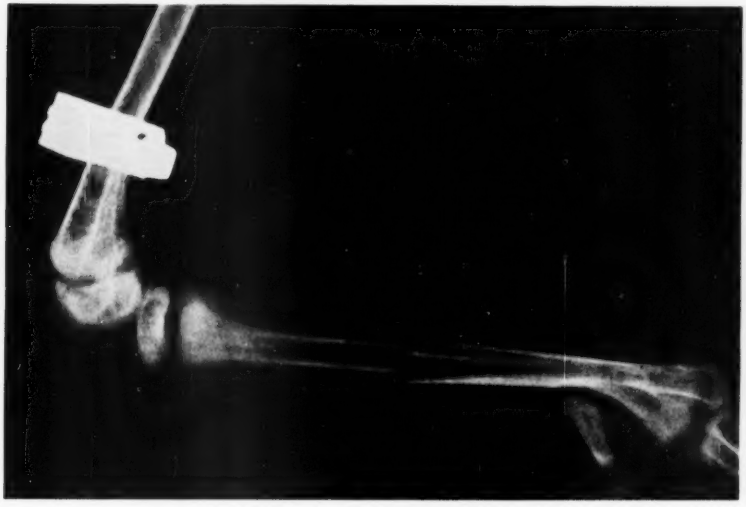


FIG. 29

Radiograph of a pathological fracture of the left first metatarsal in a three and a half-months-old chicken with insulin-induced osteogenesis imperfecta (post-natal type). Note that it is typically transverse and "subperiosteal." The fracture occurred spontaneously.

FIG. 30

FIG. 31

Figure 30—Sagittal section (×6) of a normal twelve-days-old embryo stained with toluidine blue. The cartilaginous core of the tibia has been stained deeply by the selective stain. Figure 31—Sagittal section of the tibia (×6) of a twelve-days old embryo treated with 5 units of insulin on the fifth day of incubation. Note the severe degree of degeneration in the cartilaginous core and the deformity of the tibia. The stunting in the growth of the tibia is obvious from comparison with the normal tibia (on the same scale).

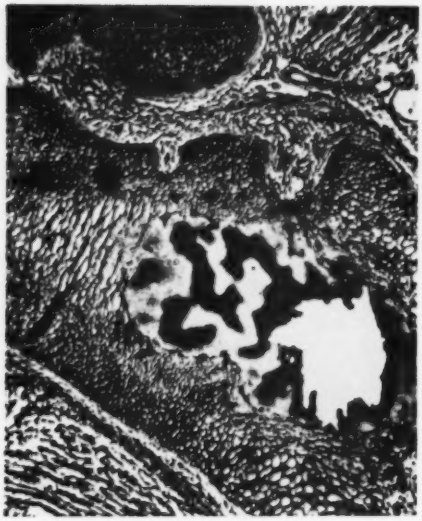


FIG. 32

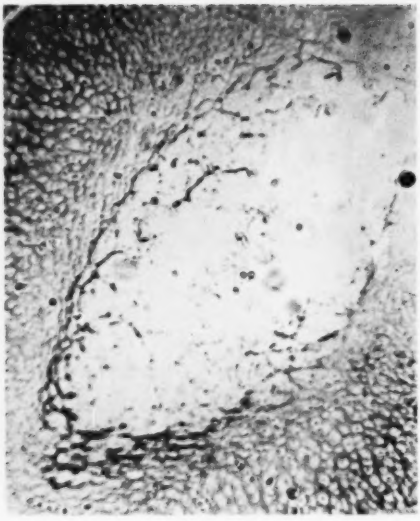


FIG. 33

Figure 32—Photomicrograph (× 100) of a section from the cartilaginous lower epiphysis of the femur of the insulin-treated embryo shown in Figure 31. Note the severe degree of mucoid degeneration with a hole in the degenerated area. Figure 33—Photomicrograph (× 100) of a section from the cartilaginous shaft of the tibia of an insulin-treated (6 units on fifth day) twelve-days-old embryo. Note the severe mucoid degeneration with a big hole in the centre of the degenerated area.

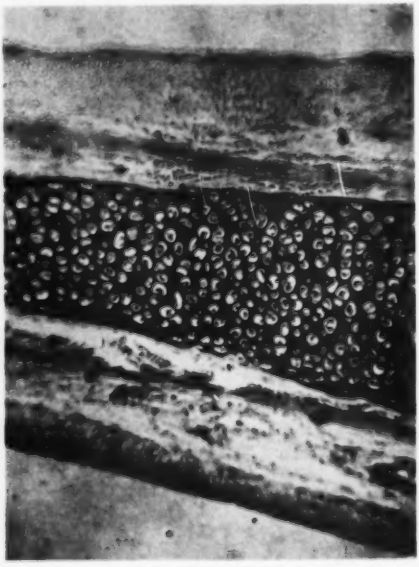


FIG. 34

FIG. 35

Figure 34—Photomicrograph (× 60) of a section from the cartilaginous core of the tibia of a twelve-days-old normal embryo stained with toluidine blue. The cartilage cells have been stained deeply and appear normal. Figure 35—Photomicrograph (× 60) of a similar section from a twelve-days-old embryo treated with 2 units of insulin on the fourth day. Note the moth-eaten appearance. The degeneration in this section is not as severe as that seen in Figures 32 and 33; the dose of insulin in this case was only 2 units.

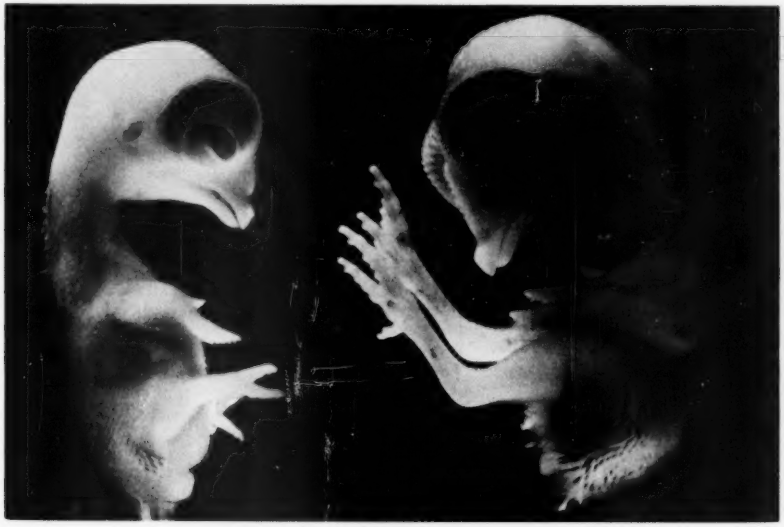


FIG. 36

Ten-days-old embryo with achondroplasia induced by 4 units of insulin on the fifth day, with a normal ten-days-old embryo for comparison. The short limbs of the achondroplasic embryo contrast typically with the nearly normal trunk to which they belong.

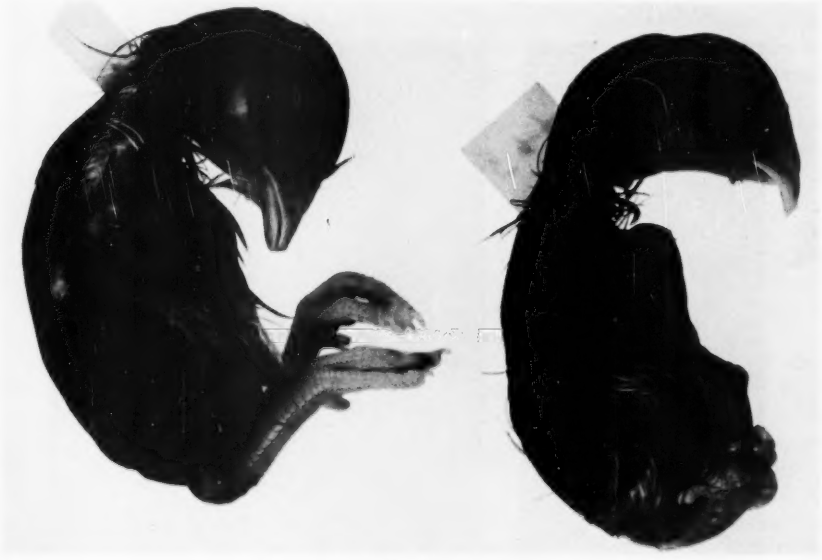


FIG. 37

Twenty-days-old chick embryo (right) showing achondroplasia induced by 2·5 milligrams of thallium nitrate injected into the yolk on the fifth day of incubation. Note the short lower beak and the typically short limbs whose proximal parts are disproportionately retarded in growth. Due to the retardation in the growth of the base of the skull, which is developed from cartilage, and the normal growth of the vault, developed from membrane, the embryo appears to be dolico-cephalic and the upper beak seems to overgrow the lower. Normal twenty-days-old embryo for comparison.

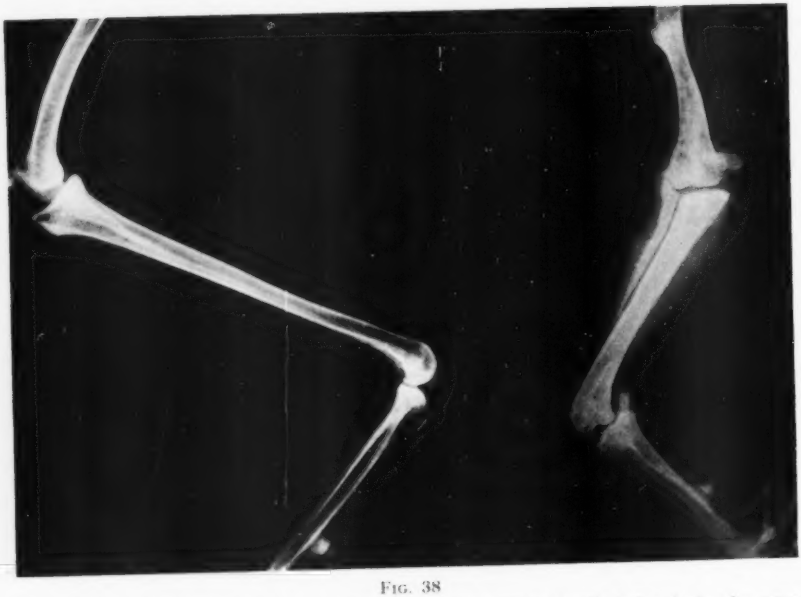


FIG. 38

Radiograph of a limb from a nine-months-old chicken showing insulin-induced chondro-osteodystrophy with appropriate control for comparison. The short, deformed bones of the limb of the insulin-treated chicken contrast typically with the radiograph of the control.

FIG. 39

FIG. 40

Figure 39.—Radiograph of chicken with insulin-induced dyschondroplasia. The lower end of the femur presents a cystic appearance. Histological appearance of a similar mass of cartilage is shown in Figure 40. Figure 40.—Photomicrograph (×100) of a sagittal section through a mass of unossified cartilage near the lower metaphysis of the femur from a chick with insulin-induced dyschondroplasia, showing a central area of degeneration with a ring of calcified cartilage surrounding it.

Associated abnormalities—Abnormalities associated with skeletal deformities included the following. *Beak deformities*—A highly arched upper beak was often associated with limb deformities (Fig. 23) and much less commonly a short upper beak and crossing of the beaks were observed. *Eye abnormalities*—Anomalies of the eyes such as anophthalmos (Fig. 5), microphthalmos and buphthalmos have been associated with skeletal abnormalities. *Genital glands*—The gonads appear to be relatively smaller in the insulin-treated chickens than those of the controls of corresponding ages. Some among the former group show marked atrophy of the germinal cells, though the interstitial cells seem to escape.

PREVENTION OF INSULIN-INDUCED ABNORMALITIES

I have injected solutions of nicotinamide and riboflavin into the yolk after making an injection of insulin, on the hypothesis that nicotinamide and riboflavin, which are known to play an important part in carbohydrate metabolism, would perhaps counteract the effects of insulin hypoglycaemia by accelerating the synthesis of the saccharides in the yolk-sac and promoting their utilisation by the embryonic tissues. I was indeed gratified to find that these substances prevented to a remarkable extent the induction of deformities by insulin. It is proposed to consider this aspect of the subject in detail in a later communication.

DISCUSSION

The question naturally arises whether the various deformities observed are due to the mechanical trauma caused by the injection or to specific action of insulin. Saline in quantities very much larger than the volumes of insulin solution, and A.C.T.H. (up to 4 milligrams per egg), have been injected, by the same technique, into hundreds of control eggs without any resulting abnormalities. Injections of substances that are known to influence ossification, such as parathormone (up to 5 units), calciferol (up to 2,000 i.u.), and radioactive phosphorus (up to 20 microcuries), have been made, also without affecting the normal development of the embryos. Insulin inactivated by the methyl-alcohol-hydrochloric method of Charles and Scott (1931) has been injected and no deformities have appeared whereas, when inactivated insulin was reactivated by alkali and then injected, the deformities have occurred. Ancel and Lallemand (1942) who had injected more than ninety substances into hens' eggs succeeded in inducing "micromelia" and beak deformities in the chick embryos only with two—sulphonamide and eserine sulphate. In view of the above experimental evidence I am satisfied that the possible mechanical trauma of injection is not a factor in causing the various deformities. In point of fact, there is adequate experimental evidence to suggest that insulin induces the abnormalities by upsetting the carbohydrate metabolism of the embryo.

Insulin, if injected during the first week of incubation, produces a definite hypoglycaemia which persists till about the twelfth day of incubation in brown leghorn and light Sussex chick embryos with which I have conducted my experiments (blood sugar estimated by Hagedorn-Jansen method). Zwilling (1948) has made similar observations, experimenting with white leghorn chick embryos and employing a different technique (Folin-Malmros) for estimating the blood sugar, after injecting different doses of insulin into the yolk. He was also able to demonstrate a close association between insulin-induced "micromelia" and the hypoglycaemia caused by the hormone. Zwilling states: "Without exception all insulin-treated embryos regain normal blood sugar levels by the fourteenth day of incubation. Apparently some mechanism of sugar control which becomes effective some time between the twelfth and fourteenth day of incubation overcomes the hypoglycaemic effects of insulin." I believe the explanation for this may very well lie in the experimental observations made by Idzumi (1924), Murray (1926) and Potvin and Aron (1927), indicating that the embryonic

liver in the chick begins to store glycogen in appreciable quantities about the eleventh day of incubation and it is only thereafter that the carbohydrate metabolism in the chick embryo is controlled by the interaction between the appropriate endocrine glands, which also begin to secrete active hormones about the same time. Presumably insulin could induce the various abnormalities before this control is established in the embryo.

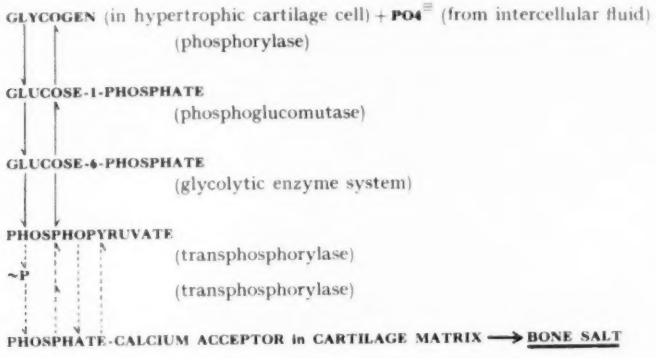
Zwilling (1951) has made further experimental observations which lend additional support to the view that insulin-induced abnormalities result from a derangement of the carbohydrate metabolism. He states: "We have demonstrated that the yolk-sac membrane contains a considerably increased amount of glycogen for several days after insulin is injected into the yolk-sac of five-day embryos. This reaction accounts for the hypoglycaemia in the embryonic circulation. The hypoglycaemia observed in the younger embryos, after injection at thirty hours, is presumably due to the same type of reaction of the yolk-sac membrane . . . The pronounced association of hypoglycaemia and rumplessness at four days may indicate that both the embryonic and yolk-sac tissues respond to insulin in the susceptible eggs; the carbohydrate metabolism of both may be altered . . . In view of the sensitivity of embryonic tissue to carbohydrate lack (Spratt 1948), it is likely that these tail anomalies ('rumplessness') may be causally related to the lowered blood sugar."

My own histochemical investigations, employing the techniques of Hotchkiss and Lison, reveal that at least two of the major carbohydrate components, glycogen and acid mucopolysaccharides (chondroitin-sulphuric acid complexes), are involved in the insulin-induced distrubances to the carbohydrate metabolism of the chick embryo. It is therefore conceivable that insulin may deprive the actively proliferating mesenchyme—which is rich in glycogen and mucopolysaccharides, according to Barfurth (1885)—precartilage or cartilage of glycogen and mucopolysaccharides, depending on the time ("critical period") at which it is injected as well as its dose, and thus may give rise to a variety of single and multiple deformities in the cartilaginous skeleton.

Now let us examine how a derangement of the carbohydrate metabolism in the embryo can affect the ossification in the cartilaginous skeleton. Since the demonstration of glycogen (*zoamyline*) in cartilage by Rouget in 1859, a number of histochemical observations of this material have been reported. With the passage of time there has grown a feeling that the presence of glycogen might have some bearing on the process of calcification. In 1885 Marchand called attention to the increase in size of the cartilage cells at the growing ends of the bones and ascribed this "hypertrophy" to an accumulation of glycogen in the cells. Hoffman and his associates (1928) have demonstrated that a "striking relationship exists between the disappearance of glycogen in cartilage and its ossification." According to Harris (1932, 1933), the "hypertrophic cartilage cells provide both the phosphatase enzyme described by Robison (1923) and glycogen which, on hydrolysis, yields hexose-phosphoric esters." Due to the interaction between phosphatase, hexose-phosphoric esters and calcium of the circulating body fluids, an insoluble phosphate of calcium is deposited into the cartilage matrix. (It may be recalled that it was in the course of my experiments to verify this hypothesis that I accidentally observed the teratogenic properties of insulin.)

More recently, the presence of glycogen in hypertrophic cartilage cells has assumed further importance as a result of the demonstration of phosphorylase activity in the epiphysial cartilage by Gutman and Gutman (1941). In 1949 Gutman and Yu put forward their concept of the role of enzymes in calcification in cartilage as follows: "Calcification in cartilage evidently is a much more complex process than mere precipitation or the simple scheme proposed by Robison. It seems clear that enzymes other than phosphatase are involved. From the combined chemical and histochemical evidence, phosphorylate glycogenolysis would appear to be an essential part of the process in its preparatory phases, and probably corresponds at least in part to what Robison called the second mechnism . . . Our experiments offer an explanation for the accumulation and disappearance of glycogen at the site of

calcification in cartilage and provide for a potential source of phosphoric ester substance for phosphatase . . . " A schematic representation of their concept of the role of phosphorylate glycogenolysis in endochondral ossification is as follows:



Follis (1949a and b) presented even more direct experimental evidence to support this concept of the relation between phophorylative glycogenolysis and ossification in cartilage. By employing special histochemical methods he showed that in normal endochondral ossification there is an inverse relationship between the presence of glycogen and the deposition of lime salts in the zone of provisional calcification. He also observed in rats (Follis and Berthrong 1949) that in markedly rachitic cartilage glycogen is present only in the more recently matured hypertrophic cartilage cells. When healing of rickets was effected by intraperitoneal injection of phosphate, deposition of bone salts was found to occur only in the matrix adjacent to the glycogen-containing hypertrophic cartilage cells and not in the area devoid of glycogen—this apparently accounting for the well-known " line " test for healing rickets. Marks and Shorr (1950) have shown that ptyalin-treated cartilage from which glycogen was removed by enzymatic digestion did not calcify *in vitro* in calcifying solutions containing phosphorus as inorganic phosphate; addition of glucose-1-phosphate to such solutions, however, restored the calcifying capacity of the ptyalin-treated cartilage.

So far, we have confined our attention to the part played by the large glycogen stores of the hypertrophic cartilage cell in the processes of normal calcification in cartilage. According to Rubin and Howard (1950), this is not the whole story. On the basis of their histochemical observations, employing Lison's technique with toluidine blue stain and Hotchkiss histochemical reaction, on a number of different calcifying and calcified structures, both normal and pathological, they have concluded that acid mucopolysaccharides (chondroitensulphuric acid complexes) in the cartilage matrix also play a specific role in the calcifying mechanism by acting like " sulphonated cation exchange resins which absorb calcium, among other cations."

On the strength of all the above-mentioned experimental evidence demonstrating the important role of glycogen of the hypertrophic cartilage cell and the mucopolysaccharides of the cartilage matrix in normal endochondral ossification, I believe it is reasonable to attribute the defective ossification in the cartilaginous skeleton of the insulin-treated embryos to an abnormal carbohydrate metabolism. Thus the possible mechanism involved in the teratogenic action of insulin may be summed up as follows. Insulin-induced hypoglycaemia may deprive the mesenchyme, pre-cartilage, and cartilage of glycogen and mucopolysaccharides, depending on the time of injection and its dose, and thus give rise not only to a variety of single and multiple deformities in the cartilaginous skeleton but also to a defective endochondral

ossification which may result in a generalised developmental disturbance of bone resembling osteogenesis imperfecta in man.

SIGNIFICANCE OF THE EXPERIMENTAL OBSERVATIONS IN ORTHOPAEDIC SURGERY

Now let us examine the significance of some of the experimental findings recorded in the previous sections. The question naturally arises: do these throw any light on the causation of congenital defects in man? It seems to me that the best way to answer this question is to discuss, first, the more important theories that have been put forward on the etiology of congenital malformations in the light of the various observations recorded in the preceding pages, and then to consider the practical application of some of my own experimental results in conjunction with those of others in order to formulate a possible hypothesis.

CURRENT THEORIES ON THE ETIOLOGY OF CONGENITAL MALFORMATIONS

Genetic theory—It has been well established that the basic laws of heredity apply not only to plants and lower animals but also to mammals, including man, and that certain pathological traits are inherited in the same manner as normal ones. However, the details of the mechanism of operation of the genetic factors are imperfectly known and it is seldom that the physician can speak to parents with any degree of certainty about the probable condition of their unborn child even when an accurate family history is available to him. In some types of congenital deformities—for example, polydactyly and symphalangism—the hereditary incidence is high whereas in others it is low. In some varieties, such as fragilitas ossium, we notice a definite familial tendency whereas others occur only sporadically. From the scientific point of view heredity is a strong argument in favour of the germplasm theory. From the clinical point of view, the aspect of eugenics is important in so far as the likelihood of transmission from the parent to the prospective children is concerned.

As pointed out at the beginning of this essay, genetic factors have, until recently, been the only ones to be studied in the field of mammalian teratology; so much so that it has often been stated that all congenital malformations in man and other mammals are determined genetically and are, therefore, inheritable. While I do not wish to minimise the importance of genetic factors in the causation of congenital defects, "clinical observation, as well as experimental work, have now shown environmental factors must be considered as teratogenic agents" (Warkany 1947). Eminent geneticists like Goldschmidt and Landauer hold similar views. With regard to the phenocopy phenomenon induced in *drosophila* by applying high temperatures at different times during development, Goldschmidt (1935) stated: "The essential point is that the normal integration of all reaction rates in the embryo is subject to interference. Such interference may be brought about by external agencies at the will of the experimentalist or by internal changes in the genes which may be catalysts or producers of inhibitors. If gene changes shift the rates of reactions during embryonic development relatively to one another, so also can external agencies." Landauer (1947) was impressed by the resemblances between insulin-induced "rumplessness" and the two types of hereditary "rumplessness," and between the micromelia and beak abnormalities of insulin-treated chick embryos and the hereditary micromelia seen in the "short upper beak" stock. He stated: "It may be assumed that either mutant genes or experimental procedures such as the injection of insulin into chicken eggs may interfere with the normal functioning of developmentally important physiological events, perhaps the elaboration of particular substances."

Needham (1942) has referred to a number of experimental observations by different investigators to prove his statement that genes could induce various metabolic changes. For example, Watchorn (1938) demonstrated that the autosomal recessive gene in the mouse *grey-lethal* gave rise to low blood phosphate, low liver glycogen and hypoglycaemia, though the muscle glycogen was known to be normal. Grüneberg (1935, 1936, 1938) has also observed in the

FIG. 41

Adduction deformity of the toes of the right foot induced by insulin. The deformity was transmitted to the offspring (Fig. 42) after mating with a normal hen. The egg was not treated with insulin.

FIG. 42

Adduction deformity of the toes of the right foot in a ten-weeks-old chicken inherited from its male parent shown in Figure 41.

FIG. 43

FIG. 44

Figure 43.—The mother of the chicks shown in Figures 44 and 45. She has club feet induced by insulin. She was mated with a normal cock and the eggs were not treated with insulin.

Figure 44.—Bilateral club feet in a five-days-old chick inherited from its mother with club feet induced by insulin.

FIG. 45

Three-weeks-old chick showing bilateral club feet inherited from the same hen shown in Figure 43. (This is the third in the series to inherit the deformity; other offspring appeared normal.)

FIG. 46

FIG. 47

Figure 46—Twenty-days-old embryo (dead in shell) with osteogenesis imperfecta (pre-natal type) inherited from both parents with similar abnormalities induced by insulin. There was a pathological fracture of the right femur. Figure 47—Another twenty-days-old embryo (dead in shell) showing osteogenesis imperfecta (pre-natal type) inherited from both parents with similar abnormalities induced by insulin. Figure 48 shows the radiograph of the skeleton of this embryo.

FIG. 48

FIG. 49

Figure 48—Radiograph of a twenty-days-old chick embryo with pre-natal type of osteogenesis imperfecta inherited from both parents with similar abnormalities induced by insulin. Note the thin cortices of the long bones and the deformities, which are, however, less marked than those seen in the original condition induced by insulin, shown in Figure 49. Figure 49—Radiograph of a twenty-days-old embryo treated with 5 units of insulin on the fifth day, showing a severe degree of osteogenesis imperfecta, for comparison with the inherited abnormality.

same mouse that there is incomplete calcification, resulting in severe skeletal abnormalities. The animals fail to grow normally and also die at weaning if a supply of a special type of food is not given during this period. I believe that all the above-mentioned observations made by various geneticists and others are significant in the light of the results obtained from experimental teratogenesis with insulin, especially in view of the fact that common factors such as hypoglycaemia, low liver glycogen, and incomplete calcification seem to play an important part in the causation of congenital skeletal abnormalities induced by abnormal genes as well as environmental teratogenic factors such as insulin. I must admit that, at present, it is only a hypothesis which needs to be confirmed by further experimental and clinical research. Nevertheless, if it were confirmed, considerable light would be thrown on the mechanism of causation of the most important group of congenital defects—hereditary anomalies—and, what is even more valuable, we might be able to prevent them.

I wish to quote the following three sets of examples given by Warkany (1947) in his chapter on "Etiology of Congenital Malformations" in *Advances in Pediatrics* which seem to lend further support to this hypothesis:—(*a*) *Cleft palates of different etiology:* (i) Mouse derived from strain in which hare-lip and cleft palate were hereditary. (ii) Rat whose mother had deficiency of riboflavin. (iii) Rat whose mother had been exposed to roentgen rays on fifteenth day of gestation. (*b*) *Syndactylism of different etiology:* (i) Mouse derived from strain with hereditary congenital defects. (ii) Rat whose mother had deficiency of riboflavin. (iii) Rat whose mother had been exposed to roentgen rays on thirteenth day of gestation. (*c*) *Microcephaly of different etiology in humans:* (i) Microcephaly genetically determined (the subject illustrated by Warkany was a boy who had two siblings with microcephaly, and a paternal grand uncle who was mentally deficient). (ii) Microcephaly in a child with toxoplasmosis. (iii) Microcephaly in a child whose mother was irradiated with roentgen rays during the second and third months of pregnancy.

"Mechanical pressure" theory—This is the oldest theory and the notion that the congenital deformities may be caused by pressure *in utero* dates back, according to many authors, to Hippocrates. One of the foremost among the contemporary protagonists of this theory is Denis Browne. I propose to deal with his views in some detail because Browne has attempted to explain a variety of orthopaedic deformities by this theory. He states: "To prove the question one way or another by direct observation is at present impossible, and it appears likely ever to remain so. In consequence I am reduced to a method that might possibly be used more in medicine than it is, the method of comparing what abstract argument shows to be the consequence of the granting of the hypothesis under test with what is found in real life" (Browne 1936). Browne assumes first of all that a "normal" newborn baby shows "obvious stigmata of mechanical compression," and then proceeds to classify the possible disorders that may befall the foetus as a result of increased mechanical pressure under the following categories:

1) *Effects of normal mechanical pressure upon a foetus in normal position*—These include: bending of the back; calcaneus position of the feet from pressure of uterine wall upon the soles; and dimples over the bony points in contact with the uterine wall.

2) *Effect of normal pressure and development of the foetus plus abnormal position*—The commonest deformities such as congenital talipes equino-varus, malposition of the toes, "postural" torticollis, and displaced ears are included in this group.

3) *Normal mechanical and hydraulic pressure plus defective development*—It is important to note that Browne says, in contrast to Jansen: "The defective development has, of course, nothing to do with mechanical influence of any kind." Jansen stated in 1912: "Thus it may be considered probable that direct amnion-pressure has the power of destroying deep-lying parts in a perfectly normal embryo—either with or without injury to the skin." Browne includes congenital dislocation of the hip, "congenital" fracture of tibia, and congenital club hands in this group. In the case of the congenital dislocation of the hip, he thinks that

there are two factors in the causation of this deformity. The first is the " abnormally shallow acetabulum " which makes the dislocation easy, though the origin of the abnormally shallow acetabulum has not been explained. The second factor is a thrust on the knee from the uterine wall against which it lies, acting along the line of the femur to drive its head above the acetabulum and backwards. Turning to " congenital " fracture of the tibia, he remarks: " Here there is almost always a faulty formation of the bones of the leg, usually an absence of the fibula." (Again, he has not explained why there is a faulty formation of the bones of the leg to begin with.) " The invariable scar over the apex of the angle in the tibia is a typical pressure dimple. As to the angle itself, if it is not an effect of the bending of the presumably weaker leg over the other, it is curious that the invariable equinus position of the foot should correspond to the force necessary, and that the point of bending should correspond to the spot just above the heel, where the other skin would catch to form a fulcrum " (Browne 1936). It is pertinent to point out here that if 5 units of insulin were injected into hens' eggs on the fifth day of incubation, 85 per cent of the surviving embryos would show similar deformities of the tibia (Fig. 16), without any evidence of mechanical pressure. As already mentioned Warkany and his associates (1943) observed similar tibial deformities in a high percentage of the offspring of rats reared and bred on a diet deficient in riboflavin. When I visited Cincinnati recently I had an opportunity to examine many of these specimens and I could not find any evidence of mechanical pressure which could have given rise to these defects. On the other hand, there was adequate pathological evidence in the tibia itself to account for the deformity, as in the insulin-induced abnormality in the tibia. One cannot deny that mechanical pressure of any sort, and for that matter, even normal movements of the embryo or foetus, as the case may be, may aggravate the original deformity due to obvious pathological changes as seen in the cartilaginous tibia (Fig. 31). I believe that emphasis should be placed on what Browne calls " a faulty formation of the bones of the leg," whatever its origin may be, rather than on his hypothetical " mechanical and hydraulic pressure." For example, the more common anterior angulation of such a tibia showing pathological changes in the cartilaginous core may very well be due to an unopposed action of the calf muscles, there being no necessity to postulate mechanical and hydraulic pressure.

4) *Normal hydraulic pressure and normal position with increased mechanical pressure*—Browne thinks that this will cause the spine to be " shortened by the acute scoliotic bends " and the muscles of the legs to become atrophied and fibrosed from interference with the circulation.

5) *Effects of normal hydraulic pressure plus increased mechanical pressure plus abnormal position*—In this group he includes " club feet of the usual type with muscle and joint degeneration, atypical talipes with muscle and joint degeneration, displaced finger showing arthrogryposis (confined to the fingers alone), spina bifida with talipes and degeneration of the muscles and joints of the legs." Browne (1936) gives the following explanation for the formation of spina bifida: " This most complicated and intractable deformity appears to me quite easily explicable under this heading. Let us imagine again what would happen if right at the start of foetal life the relation between the expanding foetus and its surroundings was disturbed, so that the bending of the back was exaggerated from its very beginning. At this time when the foetus (embryo) is barely 2 millimetres long, the edges of the neural groove are joining to form the neural tube. Any extra bending would make the sides of this groove gape at the point of the maximum curve, that is, the lumbar region. Accordingly faulty fusion would be likely, with the formation of a spina bifida at this point." Browne has not, however, indicated the nature of the disturbance which is supposed to exaggerate the bending of the back, " when the foetus is barely 2 millimetres long."

6) *Effects of increased hydraulic pressure*—Browne postulates increased hydraulic pressure for the causation of arthrogryposis. According to him the hydraulic pressure could be increased in two ways: first by the amount of fluid being too large, and secondly by the container being too small. He explains: " With such an increase one would expect that the waves of

blood sent into the foetal circulation from its own heart and the maternal one would be very readily diminished by the elastic pressure. Consequently only the muscles and viscera close to the impulse would get a full supply, and the limbs would be in a condition of reduced arterial supply combined with venous stasis. The degeneration of muscle and stiffening of the joints already described would occur just as before, but the nerves would be less liable to harm than they are in mechanical pressure." It is difficult to understand how the increased hydraulic pressure which should be transmitted equally in all directions, according to Pascal's law governing fluid pressure, can be postulated to obliterate, even partly, deeply placed arteries of the limbs without at the same time causing serious damage to the brain by pressure on the fontanelles and the thin membranous vault of the skull. Moreover, there is evidence to show that the pathology in the amnion (hydramnios, oligamnios, and amniotic bands) may be caused by the same noxious agent—for example, 3-acetyl-pyridine—which gives rise to degeneration in the affected muscles. It is interesting to note that the incidence of hydramnios in diabetic mothers is high (27 per cent) according to Oakley and Peel (1949), whereas arthrogryposis does not occur any more frequently among the children born to diabetic mothers than among other children. On the other hand, it is conceivable that those factors which are responsible for the high incidence of other congenital malformations in children born to diabetic mothers may very well give rise to hydramnios in a high percentage of cases. I have observed that cortisone, when injected into the yolks of hens' eggs, induces not only certain congenital abnormalities, such as ventral hernia, in the chick embryos but also produces oligamnios and amniotic bands. Dareste (1882) claimed to have induced hydramnios, oligamnios and amniotic bands together with developmental deformities in the embryo in the course of his numerous experiments in teratogenesis (Ballantyne 1904).

Many observers have raised objections against the mechanical pressure theory on the ground that the uterus is not a rigid chamber but one which accommodates itself, under the influence of the appropriate endocrines during pregnancy, to its contents; and twins are seldom affected. Further, the foetus is known to be constantly changing its position and moving its limbs so that continuous pressure on any particular part is hardly possible. Middleton (1934) who strongly opposed the pressure theory stated: "It is well that there should be a clear understanding of what uterine pressure can and cannot do in the way of producing deformities of the extremities. The so-called packing of the foetus in the later months of pregnancy consists in the mutual accommodation of parts physiologically unresistant, and appears to produce distortions of the limbs such as the normal slight flexion contracture of the hips and the common talipes calcaneo-valgus . . . Real and persistent deformities such as tibial kyphosis, talipes equino-varus and very many more cannot be caused by intra-uterine packing, and the mistaken impression that they can be is largely due to the fact that the position of the foetus *in utero* adapts itself to any deformity which may be presented."

The " bleb " theory—This theory has been offered to explain the developmental mechanism of deformities such as club foot, congenital dislocation of the hip, Sprengel's shoulder, cleft palate, spina bifida; and also syndromes like Laurence-Moon-Biedl syndrome, chondro-osteo-dystrophy (Morquio-Brailsford type), pleonosteosis familiaris (Léri), Turner's syndrome, cranio-carpo-tarsal dystrophy, oxycephaly, acrocephalosyndactyly, dysostosis craniofacialis (Crouzon) and others (Engel 1940, 1943).

Origin of the " bleb "—Reference has already been made to Bagg's experiments on mice employing x-radiation as a teratogenic agent as a result of which malformations such as club foot, syndactylism, polydactylism and congenital amputations were produced. According to Bagg the earliest foot defect was associated with the formation of a blister-like bleb, which raised the epithelium of the foot, usually in a localised area. This bleb was generally observed during the twelfth to fifteenth day of prenatal life and was followed by the escape of blood into the bleb and the formation of a localised blood clot.

Bonnevie (1934) investigated the bleb structures in the mice that were bred from six extracted abnormals which were sent to her in Norway by Bagg's associate, Little, in 1930 for further breeding experiments. According to Bonnevie the bleb fluid is really cerebrospinal fluid which is expelled through the foramen anterius, a pear-shaped foramen existing for a short time in the anterior part of the roof of the fourth ventricle of the embryo. She believed that the expulsion of the cerebrospinal fluid through this opening was a normal occurrence. In this case, however the quantity of the expelled fluid was abnormally high either from excessive production or deficient absorption or to a primary dysunion in the mid-dorsal line. The subcutaneous blebs so formed began to spread to the body surafce and on their paths exerted a "deleterious influence by pressure, and provoked an inflammatory reaction" (Bonnevie 1934). They were "driven by physical forces towards areas of least resistance and were arrested and retained by preformed cavities and pockets, like the orbits and limb buds." Bonnevie thought that the displacement of the blebs along the embryonic surface was probably governed by mechanical forces and above all by the elasticity of the epidermis forming the bleb roof.

Divergent views on the origin of the "blebs"—Unlike Bonnevie, Bagg (1929) attributed the formation of the blebs to "a localised arrest of development . . . associated with a perivascular lymph stasis." Keith (1940) disagreed with this view and said: "A localised arrest of development need not give rise to effusion of lymph and blood; only a localised necrosis of foetal tissue could occasion such a train of events, and the most probable cause of necrosis is a localised failure of circulation of blood. Nowhere has Bagg recorded the state of the placenta in these dysplastic embryos, although placental lesions, were they present, would not likely escape his vigilant eye." Plagens (1933) has presented experimental evidence to show that the bleb fluid takes origin from the blood stream, as will be seen later. Blister-like blebs have not infrequently been associated with the necrotic changes induced by insulin in chick embryos.

Engel (1940, 1943) attempted to harmonise, rather unconvincingly, the above experimental findings and the clinical experience, and to give "a morphogenetic explanation" for the various deformities and syndromes enumerated. On the basis of Bonnevie's observations in mice, he suggested vaguely that the localisation of the blebs may depend upon "some modifying factors or genes" and "by regular combinations of genes some deformities will manifest themselves as syndromes."

Objections to the "bleb" theory—The "bleb" theory was vehemently opposed by Plagens (1933) who experimented with the same mouse strain as Bonnevie. In contrast to Bonnevie's observations, Plagens found that there was no regular movement of the blebs along the surface of the developing embryo and that the blebs were transitory and they never formed haematomas. He observed that the number of blood cells increased considerably in the abnormal embryos, more so in individuals possessing larger and more numerous blebs. He attributed this change to an escape of the liquid part of the blood from the circulation and its accumulation in the blister-like structures which, therefore, could not have been formed by expelled cerebrospinal fluid as was suggested by Bonnevie. As mentioned above, Plagens presented experimental evidence to prove that the bleb fluid had its origin from the blood stream. On the basis of his experimental observations, Plagens concluded that the blebs, after all, played only a minor role in the production of the gross disturbance in the limb and the primary cause of the abnormalities in this mouse strain lay in the "thrombi which usually appeared two or three days later than the blebs and haematomas." He pointed out that in the photomicrographs published in Bonnevie's paper there are many examples of haematomas and thrombi. Plagens did not, however, give any clue with regard to the active agent responsible for the formation of the thrombi. It is not inconceivable that abnormal genes may induce these changes in the blood stream at critical periods during the development of the pathological descendants, thus giving rise to the primary dysplastic lesions as well as *secondary* "blebs," in the same

way as the autosomal recessive gene in the mouse *grey-lethal* has been shown by Watchorn (1938) to give rise to low blood phosphate, low liver glycogen and hypoglycaemia.

Streeter's foetal dysplasia theory—By 1930 Streeter had at his disposal sixteen cases of a condition which he designated "foetal deficiencies in foetal tissues" but which Keith preferred to call "Streeter's foetal dysplasia". Streeter (1930) believed that the dysplasia was the cause of many malformations. He ascribed the lesions, which became manifest in the foetus as it developed, to a fault inherent in the chromosomes of the fertilised ovum. Keith (1940), however, considered it more reasonable to regard the fault as lying in a temporary—or permanent—breakdown in the circulatory system in the foetus. The lesions in Streeter's foetal dysplasia may give rise to circular necrotic grooves filled with exudative tissue in which there is embedded a constricting ring or anklet of fibrous tissue or in some cases lead on to intra-uterine necrosis of the limb or digit affected and congenital amputation.

Circulatory failure theory (Keith)—According to Keith (1940), at the end of the second month of foetal life, which appears to be the period at which foetal dysplasia of the limbs usually begins, the placenta is undergoing a rapid expansion and is therefore in its most vulnerable phase of growth. Nevertheless, the results which follow circulatory failure in an early human foetus seem to differ in certain respects from those seen in adult tissues. First of all it must be remembered that it is not until the end of the second month that a cardiac circulation is fully established, though the human heart begins to beat about the twenty-fourth day of intra-uterine life, and until then the tissues are dependent on lymph seepage and not on blood supply as in adult tissues. Keith thinks that foetal tissues have a higher degree of vitality and individual response than mature tissues. Some foetal tissues, such as the fibroblasts of the skin and deep fascia, respond in a particularly vigorous manner when cut off from their blood supply.

Keith believed that the congenital dysplastic lesions such as defects of the scalp, meningoceles, spina bifida and the various degrees of anencephaly were caused by local necrosis from a circulatory failure which might be placental in origin. The failure was supposed to occur along marginal areas where capillary formation is in progress. According to Keith the lesions become manifest at two stages of development: towards the end of the first month; and at the end of the second month. These may be considered critical periods for the placental circulation. Though this theory seems attractive, we are still in the dark with regard to the cause of the localised anaemia, as the following statement of Keith's (1940) will show: "The active agent which brings about this localised anaemia and necrosis in dysplasia foetalis still awaits discovery."

Theory of muscular derangement in the mechanism of congenital deformity (Middleton)—Though congenital myodystrophy was first described by Otto in 1841 and many examples of the condition may be found scattered through the world literature since that date, it was Middleton (1934) who drew an analogy between this condition and the muscular dystrophies of postnatal life. Middleton thought that the muscular derangement was primary in the mechanism of the congenital deformity and that the errors of the bone were in the nature of structural adaptations to the primary error of the muscle. According to him the pathology of the muscular derangement might be of three types: 1) arrest of development at the myoblastic stage; 2) failure of elongation of the muscles after normal development; and 3) intra-uterine degeneration with progressive conversion into scar tissue as in myodystrophia foetalis deformans (arthrogryposis multiplex congenita). Middleton attributed the congenital angulation of the tibia which he named "congenital tibial kyphosis," to a failure of the later stages of development of the calf muscles during intra-uterine life.

Browne (1936) raised the following objections to Middleton's theory: "The suggestion that this condition (myodystrophy) is a primary spontaneous one has two obvious weaknesses. First, it assumes a totally new pathological condition. Second, it does not explain the

associated conditions: the stiffening of joints, the deformities of the feet, and the presence of the pressure dimples when the legs alone are affected, and their absence in many cases when the arms suffer too." I believe these objections have little substance. In a careful and fascinating study of the condition of the muscles involved, Middleton presented irrefutable evidence of myodystrophy in the affected muscles. The histological sections showed fibro-fatty material containing, at scattered intervals, some remnants of muscle fibres displaying degenerative changes. I have observed that 3-acetyl-pyridine (nicotinamide "antagonist"), when injected into the egg yolk in the same way as insulin, induces myodystrophy resembling the type described by Middleton. It is interesting to note that Middleton observed, in a boy of seven, congenital scoliosis caused by myodystrophy similar to the scoliosis caused by 3-acetyl-pyridine.

The atavistic theory (Bardeleben)—Bardeleben (1874) tried to explain the etiology of congenital deformities solely on the basis of atavistic throwbacks. This theory goes back to remote phylogenetic era. Oligodactyly was thought to represent an atavistic form—namely a reduction of the digits as seen in the horse. However, the idea of atavistic reduction or increase of digits was strongly refuted by Prentiss (1910) who drew attention to the fact that all mammalian ancestors were polydactylous. Prentiss has also shown that in polydactyly the extra digits do not develop from the digital rudiments and that the abnormal occurrence of six or seven digits on the usually five-toed extremities is not a reversion to type. The supernumerary toes or fingers are duplications of normal digits caused either by primary germ variation or "extrinsic influences."

The archipterygial theory (Gegenbauer)—This theory follows more or less the same trend of thought as the atavistic theory. Gegenbauer (1864) believed that it was the suppression of "primitive rays" which was responsible for the deformities. From the phylogenetic point of view the same objection can be raised—namely, that the wing of the bird which Gegenbauer mentions in support of his theory does not represent a recession but rather a progression from the common amphibian stock which marks the cross-roads between birds and mammals.

The theory based on the concept of organisers—We are indebted to the German zoologist, Spemann (1938) for the concept of organisers. In his Silliman lecture delivered at the Yale University he has given an unparalleled account of the principal processes in development (though confined to the development of the amphibia), based on the concept of organisers. According to Spemann, Corner, and others this concept of "The hierarchy of organisers in animal development" casts a flood of light upon the problem of developmental defects induced by heredity or environment. It is outside the scope of this paper to enter into a detailed discussion on the role of organisers in the normal and abnormal development of the embryo, but this is what one of the foremost contemporary embryologists has to say about the whole concept: "Thus either a bad egg in a good environment or a good egg in a bad environment can become abnormal in the same way. This is a remarkable thing in that exactly, or almost exactly, similar injuries, often of a highly specific sort, and dependent upon very special maladjustments at very particular times in the embryonic life, can result from such dissimilar causes. How this can be is to a certain extent explained by the theory of organisers . . . Indeed the action of the genes is believed to be effected by the production of catalysts, substances which speed up chemical reactions, or of inhibitory substances, and thus there may be little difference as far as the effects on an organiser centre are concerned, between the action of a deleterious gene and of a toxic solution applied by the experimenter. It should be remembered also that the injury to the reactant tissue (that which responds to the organiser) will cause failure of embryonic growth just as much as if the organiser is disturbed, so that the harmful agencies have two targets, upon either of which they may act in one case or another" (Corner 1944). It must be made clear that practically none of the experiments on organisers have so far been conducted on mammals. However, Corner states:

"We may provisionally accept the thought that in all vertebrates, including man, the development of the animal body from the egg is guided by the action of a succession of organiser centres, getting more and more specialised and more local as they succeed one another, until the whole complex system of tissues and organs has differentiated itself out of what was once an egg of very general potency" (Corner 1944).

PRACTICAL APPLICATION OF SOME OF THE OBSERVATIONS MADE ON EXPERIMENTALLY INDUCED DEFORMITIES

The various theories on the causation of congenital defects which have been discussed in the preceding pages are rather difficult to co-ordinate. In the long chain of cause and effect each theory applies to a different level. Some, such as the atavistic theory, are rooted into the remote and obscure past; others, like the doctrine of the intrinsic germ variation, are based on the ontogenesis of the embryo itself. Still others are concerned with more immediate and recent events, such as theories that refer to mechanical, vascular, serological, metabolic and biochemical factors operative within the life span of the embryo. The later the epoch to which the theory refers, the more plausible it must appear. However, the fact remains that congenital deformities vary between themselves as follows: first of all, in type, degree and time of appearance during embryonic development; secondly, in the way in which they become associated with one another in the case of multiple deformities; and lastly, but certainly not the least in importance, in their tendency to hereditary transmission. It is therefore understandable that no single theory can easily explain all types of malformations. It is just as difficult to accept any single theory without reservation as it is to reject it unconditionally.

Discussing the merits of an etiological classification of congenital defects, Steindler (1950) says, "In spite of all information collected from experimental and genetic studies, our present meagre knowledge of the causes of congenital deformities does not warrant etiological classification. We must still depend on grouping deformities purely on morphological lines. Such morphological divisions as club hands, syndactyly and congenital dislocation of the hip contain little information regarding differences in etiological factors or in the time of incipiency of the deformity. Still, as we recognise certain morphological variants, subdivisions of these groups begin to appear, based on developmental points. The congenital dislocation of the hip is an example. We accept it no longer as a morphological unit. A distinction is now recognised between a prenatal and postnatal type which is a step forward in comprehending the nature of the deformity. A similar situation exists in congenital club foot. However, such etiological subdivision is still the exception."

I believe that there are practical difficulties in classifying congenital malformations on a purely anatomical and morphological basis, apart from its being irrational. Microphthalmia, malformed ears, cleft palate and hare-lip are common congenital defects, but unfortunately the names give no indication of the groupings of associated deformities or transitional forms between them. Congenital cataract, cardiac septal defects, patent ductus arteriosus, deaf-mutism, dental defects, microcephaly and mental retardation which result from maternal rubella during the early months of pregnancy obviously cannot be grouped together on a morphological and anatomical basis, though the etiological factor is the same. Etiological classification, surprisingly advanced in 1836, mainly due to Saint-Hilaire, was given further impetus by the experimental, embryological, clinical and epidemiological studies of various workers during the past few decades. A concept of its nature has already begun to take form, though at present its extent in detail and design remains still ill-defined, and only future research, carefully planned and wisely co-ordinated between laboratory workers and clinicians, can throw more light on this admittedly complex problem. Nevertheless it is hoped that the following classification will be of some use in grouping different anatomical and morphological malformations arising from the same or similar causes, in spite of its imperfections.

Etiology of Congenital Malformations

Genetic factors

Environmental teratogenic factors

Faulty maternal diet during gestation—deficiency of calcium, phosphorus, iodine, iron, and vitamins A, B-complex, C, D (Murphy 1947).
Maternal pelvic irradiation—x-rays, radium.
Maternal intercurrent infectious diseases—rubella, measles, chicken-pox, mumps (Fox *et al.* 1948).
Maternal metabolic disorders—diabetes mellitus; hypoglycaemia due to various causes including hyperinsulinism.
Abnormalities of maternal hormonal mechanism.
Diseases and mechanical disorders of the uterus (Ingalls and Gordon 1947).
Lesions of the placenta—vascular aberrations; diseases and disorders; placenta praevia.
Toxaemia of pregnancy (Ingalls and Gordon 1947).
Tubal gestation (Mall 1917).
Intra-uterine asphyxia or anoxia (Ingalls *et al.* 1950).
Iso-immunisation (Rh., A.B.O.).
Toxoplasmosis: ? malaria.
Drugs and metallic poisons administered during pregnancy, inadequate to cause abortion but perhaps sufficient to cause malformations (Brailsford 1948).
Mechanical factors (may aggravate the original dysplastic lesions).
Other environmental factors of unknown origin.

As mentioned before, the role of some of the environmental factors enumerated above is still *sub judice*. On the other hand, it is very likely that more will be added to the list in the near future, as Gregg (1945) has predicted: "I regard rubella and its sequelae as the title of but one chapter in the full story of congenital defects; many more chapters have yet to be written."

To sum up the hypothesis: the development of an embryo, which is presumably guided by a succession of organising processes, may be interfered with during critical periods by genetic or environmental teratogenic factors. Such disturbances caused to the organiser system may, in their turn, produce metabolic, biochemical, and other changes through the intervention of hormones and enzyme systems and thus interfere with the normal development of the embryo. The resulting abnormalities in development would not occur in a random assortment, but tend to fall into certain categories corresponding to the critical stages of development of susceptible tissues and the quality and intensity of the noxious agent. Developmental malformations may result not only from arrest of growth and differentiation of the embryo as a whole, or some of its parts, as was pointed out by Stockard (1920), but also from degeneration in tissues which had developed normally up to a certain stage, as has been clearly demonstrated in the case of insulin-induced deformities (Fig. 35) and rubella-induced lenticular lesions.

Now let us see how this general hypothesis may be applied to congenital orthopaedic deformities. It will be of interest to the orthopaedic surgeon to know that it is possible to demarcate in the life of the human embryo certain critical periods which are "peculiarly associated with catastrophic changes in the development of the skeleton" (Harris 1933). The fourth and fifth weeks of intra-uterine life are definitely associated with the development of the cartilage skeleton. The seventh and ninth weeks present widespread calcification of the cartilage of the long bones as the main feature. The last two months of foetal life are marked by the rapid growth in the length of the bones, as distinct from the increase in the size of the epiphyses. The orderly progression from the mesenchymatous condensation to cartilage, and then through calcified cartilage to bone may be disturbed by genetic or environmental teratogenic factors, as explained above, and thus may result a variety of single and multiple skeletal deformities.

In the first place, a suppression of proliferation of cells in the mesenchyme which is

destined to form a limb will result in phocomelia (total absence of a limb) or ectromelia (absence of a part of a limb). Secondly, a suppression of mitosis in the cartilage during the fifth week of intra-uterine life may lead to a complete failure of development of the cartilage, resulting in agenesis of any of the long bones such as the radius or the fibula; or agenesis of the sacrum and coccyx. Thirdly, inhibition of the active process of mitosis in the cartilage at one end of the bone will lead to a partial aplasia of the long bone such as the femur of the fibula. Lastly, varying degrees of interference with the nutrition or metabolic processes of the proliferating cells of the mesenchyme, pre-cartilage or cartilage, or any disturbance to endochondral ossification may lead to a variety of abnormalities, in a manner broadly analogous to the deformities induced experimentally with insulin and other teratogenic agents.

Discussing the etiology of congenital malformations, Warkany (1947) writes: "There can be no doubt that we are witnessing a renaissance of the science of teratology. The role of congenital malformations in human morbidity and mortality is finding increasing recognition and some fundamental clinical and experimental contributions to mammalian teratology have been made in recent years . . . It is to be expected, therefore, that in the coming decades the subject will attract a great deal of attention." Though some of the insulin-induced deformities resemble human developmental abnormalities, we must await the results of further fundamental investigations, some of which are in progress at the present time, before drawing our conclusions. However, I submit that our aim should be to explain the mechanism of causation of human congenital abnormalities also on the basis of well understood metabolic, biochemical and histological changes, whether they are induced by abnormal genes or environmental teratogenic factors, rather than by flimsy subcutaneous blebs or doubtful intra-uterine or amniotic pressure.

To further this aim, we should encourage thorough examination of aborted foetuses and stillborn infants, more or less on the lines we have followed for the experimentally induced abnormalities. It is only by such investigations that we can confirm Mall's observation that 50 per cent of all aborted human foetuses show an astounding variety of developmental malformations and, more important still, we can apply the valuable knowledge gained from animal experiments to a better understanding of the etiology and pathology of human congenital anomalies. As mentioned at the outset, the greatest practical difficulty with early human embryos and foetuses is that they show post-mortem degenerative changes before accurate histological methods can be applied. This naturally emphasises the necessity of conducting all pathological examinations of these specimens with the least possible delay after abortion, natural or therapeutic. It is interesting to note that Hertig (1948) had a valuable opportunity to examine twenty-six implanted ova from surgically removed uteri, within six weeks of fertilisation of the ova. He concluded that over 40 per cent of the embryos were abnormal. A routine examination of all uteri surgically removed may enable one to obtain much valuable information.

I had an opportunity to examine the radiographs of the skeleton of a stillborn infant through the courtesy of Dr E. G. Hall, of Alder Hey Hospital, who had conducted a thorough post-mortem examination on this interesting case. The radiographs and histological sections of the long bones presented features of both osteogenesis imperfecta and dyschondroplasia. I have observed similar radiological and histological appearances in the bones of chick embryos with insulin-induced skeletal abnormalities. Harris (1933), who had an opportunity to conduct necropsies on infants with generalised developmental diseases of bone such as achondroplasia, chondro-osteo-dystrophy and epiphysial dysplasia, observed that mucoid degeneration of cartilage in place of normal calcification was the fundamental change in all these conditions. He has also come to the conclusion that the failure to maintain the hereditary form of the epiphysis as a result of mucoid degeneration is probably the prime factor in a congenital dislocation. My experimental findings with regard to the analogous abnormalities induced in chicks by insulin resemble these observations in the human.

The multiplicity and variety of skeletal abnormalities induced by a single teratogenic agent such as insulin, depending on the time of its injection into the yolk and its dose, need not perplex us. As shown already, the basic factor in the pathogenesis of the various anomalies is a derangement of the vital carbohydrate metabolism in embryonic tissues such as the mesenchyme, cartilage and bone, and insulin has been found to be an eminently suitable agent with which the carbohydrate metabolism of the developing chick embryo may be deliberately upset during the first week of incubation, before it is controlled by the interaction of the various hormones and before the liver starts to store glycogen in appreciable quantities. " It is significant, therefore, that bone appears as the outstandingly susceptible tissue in these examples of experimentally induced abnormalities, and that such physiological factors as blood sugar, hormones and vitamins appear to control the normal development of the tissue " (Editorial: British Medical Journal, August 12, 1950, p. 405). It is possible that there may be other teratogenic agents capable of inducing congenital malformations by disturbing the cellular protein, fat and other metabolisms at critical periods. Fundamental investigations on these and other allied problems are needed and it is hoped that this complex subject of congenital anomalies will attract a great deal of attention from clinicians and experimental research workers alike in the years to come. It is only by increasing our knowledge of their etiology that we can hope to prevent at least some of the developmental anomalies which cause " the death of about 23 per cent of the human race before or shortly after the time of birth and handicap a certain proportion of the survivors throughout their lives " (Stockard 1909).

SUMMARY AND CONCLUSIONS

1. The magnitude of the problem of congenital anomalies becomes evident when one takes into consideration the fact that they cause the death of approximately one quarter of the human race either before or shortly after birth, and handicap an appreciable proportion of the survivors throughout their lives. Further, a significant percentage of infants judged to be normal at birth are found in later life to suffer from "disguised" anomalies of the skeleton and soft tissues. Though the study of genetic factors leading to congenital defects has attracted a great deal of attention during the last few decades, the importance of environmental causes of human malformations has received relatively less emphasis. The association of congenital anomalies such as cataract and cardiac septal defects with maternal intercurrent infection of rubella during the early months of pregnancy demonstrates clearly that changes in the germplasm cannot always be invoked as the cause of developmental abnormalities. Congenital malformations that are sometimes genetically determined, such as microphthalmos, cleft palate, and certain skeletal abnormalities, can be caused in the offspring not only by maternal nutritional deficiencies and x-radiation but also, at least in some animals, such as chickens, rats and rabbits, by the introduction of certain substances like insulin into the environment of the embryo during its development.

2. Since very little is known of the detailed histology of the early human embryo, the histological examination of cases of perverted growth is mainly limited to aborted foetuses which, unfortunately, tend to present varying degrees of post-mortem degeneration before accurate histological methods can be applied. It is exactly in this field that animal experiments can offer valuable help. According to Mall and other embryologists the pathological changes that take place in human foetuses and those obtained experimentally in animals are not merely " analogous or similar but identical."

3. An attempt has been made to review, in some detail, the more important work which has been carried out on experimental teratogenesis, on the epidemiological implications of developmental arrests in humans, and on foetal abnormalities associated with maternal metabolic and hormonal disorders during pregnancy.

4. The technique employed for injection of insulin into the egg yolk has been described. Methods used for the estimation of blood sugar in chick embryos at various stages after injection of insulin and special histochemical techniques for localising polysaccharides in cartilage have been outlined.

5. A few salient experimental results have been tabulated, and some of the insulin-induced abnormalities have been illustrated.

6. The possible mechanism of action of insulin in the causation of the various developmental anomalies has been discussed. Broadly speaking, insulin seems to affect primarily the part or tissue which is in the most active stage of growth or differentiation at the time of the injection. Within the range of 0·005 to 6 units of insulin employed, the incidence, severity and distribution of the deformities appear to increase with the dose of the hormone. It has been observed that the hypoglycaemia caused by insulin injection is not counteracted till about the twelfth day of incubation, presumably because of excessive accumulation of glycogen in the yolk-sac membrane immediately after the injection, and because of lack of glycogen storage in the embryonic liver and the absence of active secretion in the endocrine glands concerned with the carbohydrate metabolism of the embryo. It has been suggested that this unchecked hypoglycaemia may deprive the mesenchyme, pre-cartilage and cartilage of glycogen and mucopolysaccharides (chondroiten-sulphuric acid complexes), depending on the time of injection and the dose of insulin, and thus not only give rise to a variety of single and multiple deformities in the cartilaginous skeleton but also interfere with the normal endochondral ossification, resulting in a generalised developmental disturbance of bone resembling osteogenesis imperfecta in the human.

7. Insulin-induced abnormalities can be prevented to a remarkable extent by injecting nicotinamide and riboflavin into eggs along with insulin.

8. The question of the practical application of the knowledge gained from experimental observations on insulin-induced developmental abnormalities in explaining the possible causation of congenital anomalies in humans by genetic and environmental teratogenic factors, has been discussed. It is suggested that the orderly progression from the mesenchymatous condensation to cartilage, and then through calcified cartilage to bone, may be disturbed by these teratogenic factors at critical phases during the development of the embryo, and a variety of single and multiple skeletal deformities may thus be induced.

9. A plea is made for routine pathological and radiological examination of aborted foetuses and stillborn infants more or less on the lines followed for experimentally induced deformities with a view to applying the knowledge gained from animal experiments to a better understanding of the etiology and pathology of human congenital anomalies.

10. As regards the possible prevention of these deformities, it is not always easy to offer sound eugenic advice in the cases of congenital malformations determined partly or completely by genetic factors, for two important reasons. First, it is often difficult to distinguish between genetically determined congenital anomalies and their phenocopies. Secondly, genetically determined developmental defects sometimes show surprisingly variable expressivity and penetrance. For the conditions in which both genetic and environmental factors are involved, the most profitable immediate line of attack would be on the environmental factors. A relatively simpler problem is presented by the malformations which are, for all practical purposes, entirely caused by environmental factors. Measures to prevent congenital anomalies caused by prenatal rubella, such as exposure of girls to the disease during childhood and protection of pregnant women during the early stages of pregnancy by immune serum, are under active consideration.

11. Further energetic investigation of the causes of permaturity, stillbirths, monstrosities and congenital malformations is urgently needed, before embarking on a successful programme for prevention. "The day of successful prophylaxis is not yet, but it is much nearer than seemed possible a few years ago."

Addendum—Figure 50 shows a chicken with " inherited " club feet. It is one of the offspring from the *third generation* series which show " club feet." Twenty-four brown leghorn chickens of the *second generation* (page 660) had been sent from Liverpool to enable me to continue the genetic experiments in the Bowles Orthopaedic Research Laboratory, Baltimore, and thus verify if the deformity is transmitted to the third and succeeding generations. So far it has been traced to the *fourth generation*. Though a statistically significant percentage of the few hundred descendants examined show " club feet " of varying degrees of severity as compared with controls, it is absolutely necessary to confirm this observation in larger statistical series before drawing definite conclusions from these and parallel experiments with another breed of chickens, namely New Hampshire reds.

FIG. 50

In some further recent experiments I have observed that if cortisone (Merck's cortone acetate R) is injected into the yolks of hens' eggs in the same way as insulin, it gives rise to varying degrees of *ectopia viscerae* (*exomphalos* with or without *ectopia cordis*), tight amniotis sacs, amniotic bands and blister-like blebs. These experimental findings clearly disprove the " Amniotic Theory " and the " Bleb Theory " which have been put forward to explain the etiology of congenital defects. The blebs and amniotic bands are, in point of fact, caused by the same teratogenic agents which induce the defects. Further, the specificity of action of each of the various teratogenic agents such as insulin, soluseptasine, thallium nitrate, 3-acetylpyridine, and lead nitrate (which last substance, incidentally, induces hydrocephalus, meningoencephaloceles, and meningo-myeloceles in chick embryos), has also been demonstrated by certain experiments which involved the injection of cortisone with each of the above-mentioned substances. For example, if insulin and cortisone are injected into the yolk on the fourth day of incubation of the egg, insulin induces typical limb deformities as usual, while cortisone gives rise to *ectopia viscerae*. Analogous observations have been made with respect to the other combinations also. (An abstract of my paper on these and other observations read before the Johns Hopkins Medical Society has been published in the Bulletin of the Johns Hopkins Hospital, **90,** 447.)

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SPECIMENS FROM THE HUNTERIAN COLLECTION

R. J. Last, London, England

12. The Plantar Aponeurosis (Specimen S 117 A)

The powerful central fasciculus of the aponeurosis passes from the medial and lateral tubercles of the calcaneum forwards into the sole. Over the shafts of the metatarsal bones it divides into five processes which diverge widely from each other. The digital nerves and vessels pass forwards in the gaps between them. The processes are united by transverse fibres distal to the metatarsal heads, a probable factor in discouraging splaying of the forefoot.

Specimen S 117 A

The borders of the sole are covered by a much thinner plantar aponeurosis, through which the fibres of abductor hallucis and abductor digiti minimi are visible. Each muscle is covered posteriorly by aponeurotic fibres; those of abductor digiti minimi extend, beneath the thin plantar aponeurosis, as far forwards as the base of the fifth metatarsal, into which the muscle is partly inserted.

13. The Erector Spinae Muscle (Specimens S 242 and S 242 2)

Specimen S 242—This and the following specimen demonstrate the intricacies of the erector spinae complex. *Right side*—In the lumbar region the posterior lamella of the lumbar fascia has been removed, thus exposing the sacrospinalis muscle (marked P). The muscle is fleshy towards its lateral free border, but is clad in a dense aponeurosis below and medially; this aponeurosis slides freely upon the overlying lumbar fascia. The insertion into the lower ribs is obscured by a retained sheet of the aponeurotic origin of latissimus dorsi (marked O).

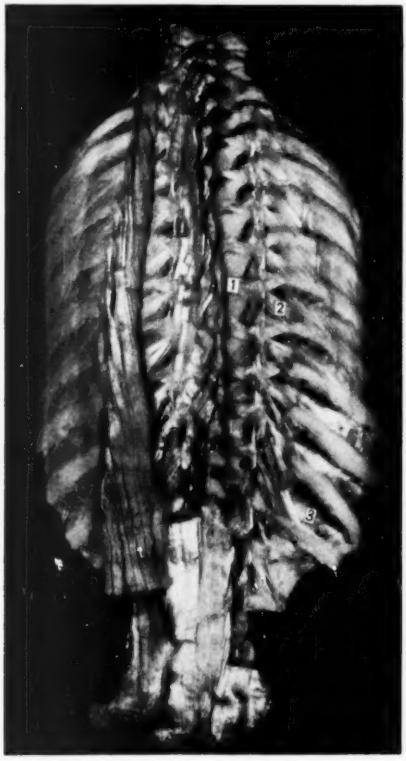
SPECIMEN S 242

Above latissimus dorsi the lumbo-dorsal fascia and the costalis muscle have been removed; the stumps of attachment of the tendons of costalis are seen along the angles of the ribs. Thus longissimus thoracis is exposed in its entirety, a powerful mass filling the gutter between ribs and vertebrae and attached to both. It divides above into longissimus cervicis and longissimus capitis. In the cervical region the semispinalis cervicis appears from below the medial edge of longissimus.

Left side—In the lumbar region sacrospinalis is partly removed and turned aside to expose some of the underlying semispinalis and multifidus fibres. In the thoracic region the costalis muscle is intact, but longissimus thoracis has been removed, exposing to view longissimus

cervicis (F) and semispinalis cervicis. The interplay of shiny tendon and bare flesh is well shown in this dissection.

Specimen S 242 2—Further points in the anatomical disposition of the erector spinae are demonstrated in this dissection. *Left side*—The lumbar region shows the stump of ilio-costalis passing up to the lower six ribs, where costalis continues upwards beneath its tendons of insertion. In the thoracic region semispinalis thoracis et cervicis is seen as a powerful mass of fibres, tendinous at their attachments, passing obliquely upwards to the tips of the spinous processes. Between semispinalis and costalis the fan-shaped levator costae muscles can be seen.



SPECIMEN S 242 2

Right side—The levatores costarum (marked 2) are here exposed in their entirety. These sturdy little muscles do not belong to the erector spinae group, being supplied by branches from the anterior primary rami (intercostal nerves), whereas the erector spinae mass is supplied segmentally by posterior primary rami of the spinal nerves.

The rotatores spinae (marked 1), existing only in the thoracic region, are well seen. They lie deep to all the rest of the erector spinae mass. Each passes from the upper part of the root of a transverse process to the lower border of the lamina of the vertebra above; because of the declination of the laminae the muscles lie transversely, at their greatest mechanical advantage.

PIONEERS OF OSTEOGENY

CLOPTON HAVERS

JESSIE DOBSON, LONDON, ENGLAND

Recorder, Royal College of Surgeons of England

The name of Clopton Havers has been associated for 160 years with the spaces or canals which traverse the compact bone tissue. In view of the fact that Haversian canals are known to every student of anatomy, it is somewhat surprising that so little is known about the man who described them. The name of Clopton Havers's father was Henry and it seems likely that he was the non-conformist clergyman, a native of Essex, who served as Chaplain for a time to the Earl of Warwick and was Vicar of Chipping Ongar about the year 1643. He was later appointed minister at Fifield (1649–50) and Rector of Stambourne in 1651. After the restoration of Charles II in 1662, he was ejected from the ministry for his non-conformist views. Clopton Havers was born in the year 1657 and nothing is known of his early education except that Richard Morton was his tutor. Dr Morton was also a non-conformist divine and he had served as Chaplain at New College, Oxford. He was forced to give up his clerical post when the Act of Uniformity was passed in 1662 and he then entered the medical profession. In 1670 he received the degree of Doctor of Medicine at Oxford and eight years later was elected a Fellow of the Royal College of Physicians. It was to Dr Morton, therefore, that Clopton Havers was most indebted in the early stages of his career. In 1668 he was enrolled as a student at Catharine Hall, Cambridge, and he studied there for a time. He left the University, however, without taking a degree and the next known fact of his life is that on July 28, 1684, he was admitted as an Extra-licentiate of the College of Physicians of London. This meant that he had authority to practise medicine anywhere in England except in the city of London or within seven miles of it, with the further proviso that he could settle in Oxford or Cambridge only if he held a special licence or had obtained a medical degree. In the following year, 1685, Havers, according to the "Album Studiosorum," was enrolled as a student at the University of Utrecht and presented a thesis entitled "De Respiratione" which gained him the degree of Doctor of Medicine of that University. This work was dedicated to his father and to Richard Morton. Figure 1 is a reproduction of the Title Page from a photostat copy of the thesis kindly presented to the Hunterian Museum of the Royal College of Surgeons by the Librarian of the University of Utrecht in November 1951.

On November 17, 1686, Havers received the distinction of being elected a Fellow of the Royal Society and he was admitted on December 15 of that year. The following three extracts, reproduced by kind permission of the Officers of the Royal Society, from the Journal Book of the Society give the details of his election:

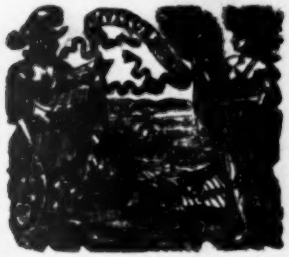
June 23, 1686: "Dr Clopton Havers, Mr Tho. Molineux and Mr John Harwood were propounded to the Society as candidates for election."

November 3, 1686: "... then the Society being a sufficient number Proceeded to the Election of three Gentlemen formerly proposed and approved by the Council whereof Dr Clopton Havers being unknown. Mr Aston he refus'd to give his ballot either in the Negative or Affirmative by which means the Election came to void, and Mr Aston desir'd that the same might be recorded which the Vice-President order'd accordingly ..."

November 17, 1686: "... Dr Clopton Havers was Balloted and chozen."

The President of the Society at this period was Samuel Pepys.

DISPUTATIO MEDICA
INAUGURALIS
DE
RESPIRATIONE,
QUAM
PRÆSIDE DEO TER OPT. MAX.
Ex auctoritate Magnifici Rectoris,
D. JOHANNIS MUNNICKS,
Reip. Ultrajectinæ Poliatri, atque in inclytâ ejusdem Academiâ
Medicinæ Anatomes & Botanices Antecessoris Ordinarii,
NEC NON
Amplissimi Senatus Academici consensu & Almæ
Facultatis MEDICÆ *Decreto,*
PRO GRADU DOCTORATUS,
Summisque in MEDICINA Honoribus &
Privilegiis ritè consequendis,
Eruditorum examini subjicit
CLOPTON HAVERS, Londinensis.
Ad diem 3. *Julii, horâ locoque solitis.*



TRAJECTI AD RHENUM,

Ex Officinâ *FRANCISCI HALMA*, Academiæ
Typographi Ordinarii, cIↃ IↃc Lxxxv.

OSTEOLOGIA NOVA

It was not until December 22, 1687, that Havers became a Licentiate of the Royal College of Physicians and was able to practise in London (probably in Fenchurch Street). He now made the study of anatomy his special interest and at meetings of the Royal Society he delivered the following papers: August 7 and October 23, 1689, "The first Discourse of the Membrane, the Nature, Constituent Parts, and Internal Structure of the Bones"; October 30 and November 13, 1689, "The second Discourse of Accretion and Nutrition"; January 29, 1689, "The third Discourse of the Marrow"; November 20 and 27, 1689, "The fourth discourse of the Mucilaginous Glands"; August 13, 1690, "The fifth Discourse of the Cartilages." These five lectures were published as a book in 1691, under the title *Osteologia nova, or some New Observations of the Bones, and the Parts belonging to them, with the manner*

of their Accretion and Nutrition. Another English edition appeared in 1729, twenty-seven years after the death of the author. The Epistle Dedicatory is to the Right Honourable Thomas, Earl of Pembroke, President of the Royal Society, and there is also a dedication to Richard Morton, in which he makes the following acknowledgment of his great debt to his former tutor: "I do therefore, as an expression of that Respect and Gratitude which are due from me, humbly present you with these Discourses: and although I shall never be able to satisfy that Debt which I have contracted; yet this will be a demonstration of my inclinations to be Just and Grateful. And there is no one can be insensible how far I am in Justice bound to render to you that, which is an account of the Talent, which you, Sir, have intrusted me with, and so far as I am capable, taught me to improve." The book was very well received both in England and on the Continent, and three editions in Latin (Frankfurt 1692, Amsterdam 1731, and Leyden 1734) are some evidence of the esteem with which it was regarded. Lilly Butler, Minister of St Mary Aldermanbury, mentioned this work in the sermon that he delivered at the funeral of Clopton Havers: "Out of this Book Dr Baglivi, when he stood for Anatomy Professor in the Sapienza at Rome, took his Lecture. This, after he was chosen out of seventeen Candidates, he publickly owned before the Cardinals and other Electors and wrote a Letter of Thanks to our learned Author for his Chair when he sent him his Praxis." French reference books do not seem quite so enthusiastic about it, however, and point out that though many of his findings had been accepted as original, in actual fact he was not the first to draw attention to them.

In the Annals of the Barber-Surgeons, an entry under the date June 30, 1698, reads as follows: "Ordered that there be an Anatomy Lecture called Gale's Anatomy, Dr [Clopton] Havers and Dr Hands being put in nominacion for reading of the same. Dr Havers was choosen for three yeares to read on the second Tuesday, Wednesday and Thursday in July next by three of the clock in the afternoone and to have thirty shillings for his paines and the remainder to be disposed of by the Committe." The Gale Lectures had been founded in 1655 by Mr John Gale, who left an Annuity of £16 to the Company of Barbers and Surgeons for this purpose, and as the records do not show the appointment of any previous lecturer, Dr Havers appears to have been the first to hold this position. As presumably the annuity had been accumulating for over forty years, and as the lecturer received only thirty shillings out of the £16 available, it seems that the "Committe" was a little niggardly in their remuneration. The Records do not reveal how they disposed of the rest of the money. A further entry in the Annals on December 14, 1699, announces that "Dr Hans and Dr Havers were put in nominacion for Reader of the Ventera Lecture in the roome of Dr Tyson" (who had recently retired).

One other publication by Havers is available. This is entitled "A short discourse concerning Concoction" and it appeared in the *Philosophical Transactions of the Royal Society* in 1699 (Vol. 21, No. 254, p. 233). Possibly too much of his time was occupied in the exercise of his profession to permit any further great literary efforts after the writing of his book in 1691, but certainly no facts are available to fill in the gap between this date and 1698. In 1702 was published a new edition of Spaher and Remmelin's, *A Survey of the Microcosme, or the Anatomy of the Bodies of Man and Woman*, edited and corrected by Havers. This must have been his last work, for in April 1702 he was afflicted with a malignant fever which proved fatal. He was buried at Willingdale Doe in Essex, in the grave of Thomas Fuller, a former rector of the parish, whose daughter he married. In the same grave are the bodies of six of his children, none of whom lived more than three years. The following extracts from Lilly Butler's funeral sermon give some estimation of his character: "He was a most respectful, dutiful son to his aged Father, frequent and liberal in making his acknowledgments to him for his ingenuous and chargeable Education, and in a late Fit of Sickness readily left all his other Business to his own considerable Loss and attended upon him for three weeks together in the country, with the Care and Service and Affection of a Physician, and Nurse and Child."

. . . " Having engag'd himself in an honourable and useful Calling, he faithfully persued the Designs of it, as one who remembred the account he must give to the Maker of those Bodies he had undertaken the care of, and truly *Watched for their Lives*. He took a great deal of Pains to improve himself in that Knowledg which was necessary to qualifie him for a laudable discharge of so great a Trust." . . . " His Countenance was grave and serious, without any Lines of Sowreness or Affectation; his Speech was soft and obliging, without any Air of Conceit or Flattery; his Behaviour gentile and courteous, without any Appearance of Art or Design." Dr Butler likened him to St Luke and said that " he was not only esteemed by his Patients for his great abilities and care and diligence, but exceedingly beloved too for his amiable Temper, his obliging Tenderness and his most winning and excellent Vertues." This funeral oration was later printed and dedicated to Mrs Dorcas Havers, the widow.

For the following record of the interment, taken from the register in Willingale Church, the writer is indebted to the present Rector, the Rev. C. A. Howell: " Clopton Havers, M.D., was buried April 29th, 1702, in what was made of sheep's wooll only and affidavit thereof made and delivered the same day." This custom of burial in wool was in accordance with a law passed in 1666 in the interests of the wool trade, and the following is an extract from the Act: " For the encouragement of the woolen manufacture of the kingdom, noe person shall bee buryed in anny shirt, shrowd or sheete made of wool mingled with flax, hemp, silk, hairs, gold or silver or any other than what shall be made of wooll onely or bee putt intoe anny coffin lined or faced with anything made or mingled with flax, hemp etc. upon paine of the forfeiture of the summe of five pounds, toe bee employed for the use of the poor of the parish when such person shall be buryed." This law remained in force until 1814. From the same parish records comes the information that Mary, the daughter of Dorcas Havers, the widow, was buried at the same church on May 6, 1702, only a week after her father's interment. Another entry records the burial of a Clopton Havers, presumably the doctor's son, on November 7, 1709.

In the introduction to the *Osteologia nova*, Havers states his reasons for making this investigation as follows: " As no Faculty has received greater Additions to its Improvement in this last Age than Physick, so no part of that has been more tempting, or more successfully pursued than Anatomy. The Dissections of many preceding Ages turn'd to a small account; so that many of the most admirable Contrivances of Nature and of the greatest Wonders in the lesser World, were inobserv'd; till the Curiosity of some ingenious Men, animated with the hopes of some new Discoveries, put them upon farther Enquiries; in which their Industry and Felicity carried them so far, that the Existence of some parts before unknown, the Nature, Structure and Use of others, began to appear. But although the Security and Observations of our Age about some of the Parts have been very accurate, we have been only coasting about others; particularly about the internal Fabrick, and some other things of the Bones our Searchers have been careless, our Notice slight and transient: not but that they deserve our strictest Enquiry and serious Remarks; for I do not see but the Almighty Architect has equally demonstrated His Divine Skill in the whole structure of these Parts which He has made of grosser Matter, as in the Formation of those which consist of sifted and more refined Particles. And how curious the Hand of Heaven has been in the Framing and Ordering of this Timber-work of our Bodies, may perhaps appear a little from this Discourse."

HAVERSIAN CANALS

The particular concern of the present paper is to give the original description of the " canals " which is to be found on page 43 of the English Editions and on page 47 of the Latin Edition published in Amsterdam in 1731: " In the Bones, thro' and between the Plates, are formed Pores, besides those which are made for the Passage of the Blood-Vessels, which are of two sorts; some penetrate the Laminae, and are transverse, looking from the Cavity

to the external superficies of the Bone; the second sort are form'd between the Plates, which are longitudinal and streight, tending from one end of the Bone towards the other, and observing the course of the bony Strings. And that I may not be thought to pretend to the discovery of what no other mens Eyes can discern, because they are generally very difficult to be observ'd, unless it be the transverse Pores in the internal Lamell, I have the pieces of two Bones, which I have brought along with me; in one of which the transverse, in the other the longitudinal Pores are very visible with the help of an ordinary magnifying Glass." He observed that the transverse pores were more numerous in those plates of bone which lay nearer the cavity and, furthermore, that they were so arranged that they did not form a continuous passage from the cavity to the exterior, which arrangement would have tended to destroy the rigidity of the bone. These transverse pores are not arranged in any kind of pattern, but have a "seeming irregularity" which tends to preserve the necessary strength of the bone tissue. The longitudinal pores are more difficult to see, but are best observed in the ribs. Havers assumed that the use of these pores was solely for the diffusion of the "Medullary Oil" for, he says: "About these passages I was particularly strict in my enquiry, whether they were not formed for Blood-Vessels, tending either to or from the Marrow: and although some of the Medullary Veins have Pores, by which they penetrate into the substance of the Bone, yet I made my self certain, that these Pores, for the generality of them which I examined, had no Vessels which passed into them." In this, of course, Havers has since proved to be wrong, for later studies showed that the canals were indeed formed for the passage of blood vessels, so that his ingenious theory that the "porosity" decreased from the cavity towards the outside of the bone because the amount of lubricating medullary oil carried by the canals would necessarily grow less as the exterior was approached, is no longer tenable.

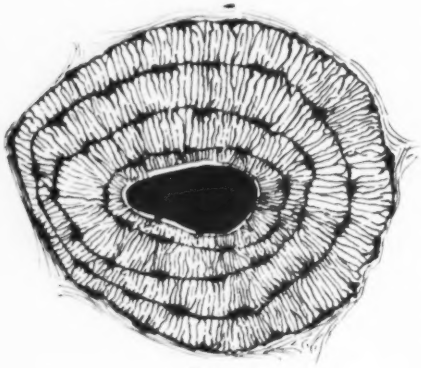


FIG. 2

It seems very likely that Anthony van Leeuwenhoek, the pioneer microscopist, had already observed these "canals" in bone, for in his letter published in the *Philosophical Transactions of the Royal Society* on September 21, 1674, he makes the following statement: "I have several times endeavoured to observe the parts of a Bone, and at first I imagin'd, I saw on the surface of the Shinbone of a Cow several small veins (which bone I still keep by me); but I have not found it since in any other bone" . . . "Afterwards I viewed the Shinbone of a Calf, in which I found several little holes, passing from without inwards; and I then imagined, that this Bone had divers small pipes going longwayes." Leeuwenhoek makes no other comment on this observation and so it must remain doubtful whether the structures he saw were actually those that later became known as Haversian canals.

The place that Havers occupies as a pioneer in osteogeny and the importance of his major work can only be estimated in relation to the times in which he undertook his laborious investigations into the "Framing and Ordering of this Timber-work of our Bodies." The *Osteologia* occupies a permanent place in literature since it was a work filled with bold speculations based, for the most part, on careful reasoning from the results of ingeniously contrived experiment and accurate observation. Havers was no copyist and he rightly named his work as *Osteologia nova*. That his canals contained blood vessels and not merely medullary oil as he contended and that they had probably been known previously to Leeuwenhoek does not detract from the merits or the originality of his observations at a time when the

dissemination of scientific knowledge was of necessity restricted. Nor must we minimise the importance of his discovery of the penetrating periosteal fibres afterwards known as Sharpey's fibres (1848). These fibres he describes as "fibrillae or threads," and that he appears at times to regard them as being nervous in function is probably due more to his usage of the term "nerve" in its original sense of a sinew, a tendon or a string, than to his failure to realise their true nature. That Portal should rather grudgingly recognise the originality of Havers and that he should stress his incomplete acquaintance with contemporary literature must not be taken in disparagement of the work of a man who, while in the active practise of his profession, produced a work that breathed a new spirit of experiment and speculation into the study of osteology.

Figure 2 is a drawing by Professor F. Wood Jones of a typical Haversian canal system, modified from Sharpey. The illustrations in the *Osteologia nova* are too diagrammatic and indefinite to justify reproduction here.

The writer wishes to acknowledge with sincere gratitude the generous help given by the following: the Library staff of the Royal College of Surgeons of England, the Royal College of Physicians of London, the Royal Society, the British Museum and the City of Westminster Public Library; Dr P. S. Breuning, Deputy Librarian of the Bibliotheek der Rijksuniversiteit te Utrecht; and the Rev. C. A. Howell, Rector of Willingale, Ongar, Essex.

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IN MEMORIAM

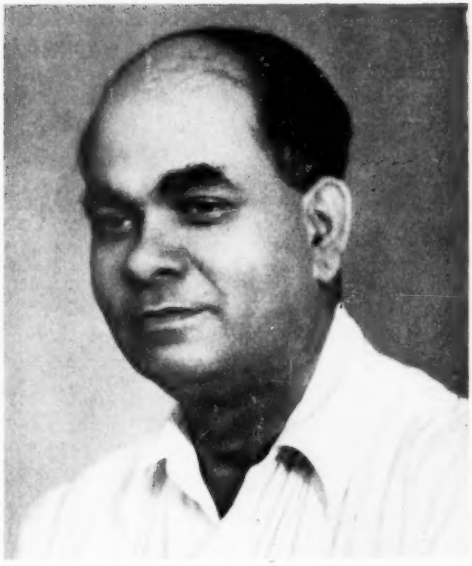
HAROLD ETTRICK MOORE, O.B.E., M.B., Ch.B.

1878–1952

Harold Moore of Crewe, fellow of the British Orthopaedic Association, and servant throughout his life of the London Midland and Scottish Railways as their consultant surgeon, hid his light under a bushel. Almost unknown as he was in this country, and still less overseas, he made a powerful contribution to the development of rehabilitation services in Great Britain. His lack of recognition arose only from his modesty and reticence. The fact is that rehabilitation and re-employment of injured workmen, in place of weekly compensation and lump-sum settlement with still remaining disability, gained greater impetus from this pioneer than from almost any other surgeon in this country. He recognised the psychological as well as the physical aspect of disability—and he recognised it thirty years ago. He was indeed a pioneer, and from his conviction he worked hard to remedy the obvious failures of County Court settlements.

During the last war he was Consultant Adviser on Rehabilitation to the Royal Air Force and Special Consultant in Rehabilitation to the Royal Navy; he gained recognition in the Order of the British Empire; but even before that he had made his contribution. It was his work in Crewe, stimulated and encouraged by Gwynne Maitland of Liverpool, that was the beginning of the rehabilitation now recognised so generally to be an essential part of the medical services of Great Britain.

R. W.-J.



MANGALORE GORPAL KINI

1893-1952

Dr Kini died on August 22, 1952, at his residence in Bombay. His sudden death at the age of fifty-nine years, while still in the full swing of work, came as a stunning blow to his large circle of friends and to the medical profession in Bombay.

Dr Kini was born at Mangalore in the South of India in 1893. Receiving his early education in Mangalore, he graduated in medicine with distinction in 1919 from the Madras Medical College. Circumstances forced him to accept an appointment in the Provincial Medical Service of Madras. He saw action in the Afghan War of 1919 and was awarded the Afghan War Military Cross for distinguished service. He subsequently worked as a teacher in surgery at the Madras Medical College till 1928. The same year he left India for purposes of higher study in the United Kingdom. He studied orthopaedics under Sir Robert Jones in the famous Liverpool School and visited the well known orthopaedic institutions on the Continent.

On his return to Madras in 1930 he organised the first orthopaedic department in the Madras General Hospital. In 1932 he was transferred to the Andhra University at Vizagapatam as professor of surgery, where he continued to develop his speciality. In 1941 he was brought back to Madras and appointed superintendent of the newly established Stanley Medical College, acting also as professor of surgery and orthopaedics. He held these posts till his retirement from service in 1948. Retirement having been forced on him at the age of fifty-five years, when he was really mature and capable of giving his best, he began to look around

for an opportunity to employ his talents in a suitable direction. He was offered high military rank and salary by the newly established Military Medical School in Poona, but he refused this post as his heart was set on orthopaedics. Instead, he accepted the invitation from Bombay to take charge of the institution started by Mrs Ismail and known as the Society for the Rehabilitation of Crippled Children. He soon became the moving spirit of the institution. His loss to Madras was a gain to Bombay. When the Society built a Children's Orthopaedic Hospital he was appointed its Director. He held this post with distinction until his death.

One particular feature of Dr Kini's work deserves special mention. He never accepted busy private practice and was thus able to devote sufficient time to the minute study of every case that came under his care. He kept detailed records of all his patients with photographs, photomicrographs and prints of radiographs upon which his numerous publications were based. In consideration of his published works he was awarded the Fellowship of the American College of Surgeons.

In 1947 he was president of the Association of the Surgeons of India of which he was a founder member. He was also president-elect for the current year for the Indian Chapter of the International College of Surgeons.

Dr Kini's work and worth cannot be judged by a mere enumeration of his academic attainments. Lack of funds is a great handicap to almost all surgeons in India who are attached to public hospitals, in their attempts to do research and original work. Dr Kini rose above these difficulties. He was indeed one of those rare individuals of whom it can be said in the words of Kipling that he did the work which lay under his nose with tools that lay under his hands.

R. N. C.

PROCEEDINGS AND REPORTS OF UNIVERSITIES, COLLEGES, COUNCILS AND ASSOCIATIONS

GREAT BRITAIN

ROYAL COLLEGE OF SURGEONS OF ENGLAND

LAMING EVANS RESEARCH FELLOWSHIP

A research fellowship of the value of £4,500 is open to medical and scientific graduates of the United Kingdom who will devote themselves to research in orthopaedic surgery. Applicants for the fellowship must hold a medical qualification registrable in the United Kingdom or a University degree, not necessarily medical. The Fellowship is of the annual value of £1,500, renewable up to three years at the discretion of the Council of the College. Applicants for the Fellowship should give details of their proposed research, state whether or not they propose to use the facilities of the College, and attach letters of recommendation from their medical school or university. Further details may be secured from the Secretary of the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C. 2. We can only trust and believe that some young surgeon or scientist will find here the opportunity he has needed to make a great contribution.

VICE-PRESIDENT OF THE COLLEGE

Sir Reginald Watson-Jones has been elected Vice-President of the College.

UNIVERSITY OF OXFORD

NUFFIELD ORTHOPAEDIC CENTRE

Within the last year a new wing has been opened in the Nuffield Orthopaedic Centre which has enabled both the staff and the work of the Centre to be increased. The new histological laboratory included in this extension has freed the old laboratory for conversion into a room largely devoted to experimental angiographic work, and a valuable addition has been a viewing room in which it is possible to display many large radiographs at one time; this has facilitated the review of large series of both clinical and experimental cases. A building for the housing of animals containing an operating theatre for experimental surgery is now under construction and will shortly be ready for use; it will allow a greater activity to those members of the Centre who are at present pursuing in animals the experimental approach to such clinical problems as bone growth, scoliosis, union of fractures, fat embolism and osteoarthritis in the Nuffield Institute for Medical Research at Oxford.

Lectures—The following lectures have been given at the Centre in the last academic year. Dr R. Judet (Paris), "Treatment of Osteoarthritis of the Hip by Arthroplasty"; Dr D. C. Sinclair (Oxford), "The Scope of Neurohistology in Relation to Pain Sensibility"; Mr M. C. Wilkinson (Black Notley), "Principles of Treatment in Skeletal Tuberculosis"; Dr A. G. Ogston (Oxford), "Laboratory Studies on Synovial Fluid"; Dr F. Schajowicz (Buenos Aires), "Clinical and Pathological Aspects of Giant-cell Tumours of Bone"; Professor G. Wiberg (Lund), "Shelf Operation in Congenital Dysplasia of the Acetabulum and Subluxation and Dislocation of the Hip"; Mr E. A. Nicoll (Mansfield), "Traumatic Dislocation of the Hip." Reports by members of the Centre on the results of their own investigations were: Dr M. Agerholm, "Serum Treatment in Poliomyelitis"; Professor J. Trueta and Mr M. H. M. Harrison, "Etiology and Pathogenesis of Osteoarthritis of Hip"; Mr E. W. Somerville, "Rotational Lordosis of the Spine"; and Mr J. C. Scott, "Results of Treatment in Infections of the Hand." The last lecture of the year was given by Professor J. Trueta on "Reflections on the Life and Work of G. R. Girdlestone."

In July the Centre had the pleasure of entertaining a group of fifty-six visitors who had previously attended the Joint Meeting of the Orthopaedic Associations of the English-speaking world and who paid a two-day visit to Oxford. Apart from the presentation of clinical and scientific papers and the demonstrations at the Wingfield-Morris Orthopaedic Hospital, the members of the Centre were able to enjoy the company of the visitors at dinner in Hall at Christ Church. Lord and Lady Nuffield were guests of honour, and Professor A. D. Gardner, who presided,

welcomed the visitors in the name of the University of Oxford. The health of the visitors was proposed by Professor J. Trueta and replied to by Mr A. Gillies, President of the New Zealand Orthopaedic Association.

UNIVERSITY OF LIVERPOOL

"ORTHOPAEDIC DAY"

Overseas visitors were entertained at Liverpool on July 9, 1952, as briefly reported in the last issue of the Journal (page 484). The day started with the arrival at 9.20 a.m. of the overseas visitors and their wives. They were received at the Medical Institution.

Debate.—After packing off the wives to Speke Hall the visitors and hosts settled down in the Lecture Theatre to debate "That Modern Advances in Internal Fixation will Render Obsolete the Use of External Splints in the Treatment of Fractured Bones." Professor Bryan McFarland was in the chair.

The debate was opened by *Mr Lloyd Griffiths* in a brilliant speech which struck the right note of mingled gravity and slightly exaggerated fantasy. In the course of his remarks he coined

Mr Esmond West, president of the Australian Orthopaedic Association, addressing the audience before unveiling the memorial plaque (inset) to Hugh Owen Thomas, Robert Jones and T. P. McMurray.

the word "surgonds" to describe semi-amateur surgeons who tackled operations beyond their proper scope. *Mr Norman Roberts* replied in similar vein, and drew on Barrie to illustrate a particularly pungent point about people playing with things they did not properly understand, using "Slightly soiled" as his main character. *Mr Robert Roaf* seconded the motion in an outspoken and striking speech in which the insincerity of the opposition was ruthlessly exposed. *Mr Goronwy Thomas* seconded the opposition, and pointed out the resemblance which some orthopaedic surgeons bear to the ostrich, in that not only have they an incurable predilection for bright metallic objects but also bury their heads in the sand while no doubt scrutinising intently their own screw-holes. To such he gave the enchanting name of "ostro-surgeons."

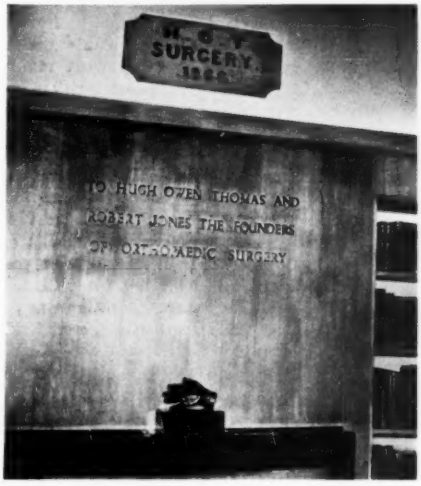
In the general debate *Dr Leo Mayer* pleaded for a balanced outlook, and recounted the history of a case treated on the transatlantic telephone. *Dr Favreau* of Montreal described the successful use of intramedullary nails in five newborn infants with birth fractures of the femur—an argument which, as he said, was both for and against the motion. (The Chairman gripped the table and said nothing.) *Mr John Charnley* (Manchester) claimed that although bone, being largely dead, could be treated with scant courtesy, periosteum, which was very much alive, should be handled

with reverence. He was developing this thesis in a strong speech for the motion, but in the end his cheek could no longer contain his tongue! *Dr Sœur* of Brussels gave an account of the general improvement in results of fractured femora since the intramedullary nail replaced plaster-of-Paris. *Dr Hamilton Bell* of Cape Town pointed out the advantages of using the nail to treat more fractures than he had beds for. *Mr Guy Pulvertaft* (Derby) said that Mr Lloyd Griffiths's speech had been so brilliant that he could not resist supporting him. *Mr Colquhoun* of Melbourne said he was on both sides, but he had to admit that the Liverpool School had done Australia some good. *Mr T. King* (Melbourne), *Mr F. C. Dwyer* (Liverpool) and *Mr E. F. West* (Adelaide) pointed out the danger of a procedure attractive to inexperienced people. *Dr Garceau* (Indianapolis) had been so self-sacrificing as to sustain three separate fractures during twenty years—the neck of the femur, the spine and the ankle. All had been neglected (or perhaps one was treated by Red Indians using birch bark and mud). He seemed very well and agile in every way, and thought that " premeditated, wilful, skilful neglect " might have a place.

On the vote the motion was defeated by thirty-three to twenty. The Chairman acceded to the wish of the members and made no comments on the debate, but instead showed cinematograph films of Sir Robert Jones and Professor T. P. McMurray—and then photographs of a patient, still alive, who in his childhood was treated for hip disease by Evan Thomas, the father of Hugh Owen Thomas.

Memorial to Hugh Owen Thomas, Robert Jones and T. P. McMurray—Lunch at University Staff House with the Vice-Chancellor, Dr Mountford, in the chair was followed by a short session in Great George Square. On the corner originally occupied by Number 11 Nelson Street a plaque had been erected on the wall of the new building which had arisen out of the ruins of the old surgery destroyed by an enemy bomb in May 1941. This plaque commemorated the three great men who had occupied Number 11 Nelson Street. It had been given by the Australian Orthopaedic Association to the Liverpool School of Orthopaedics. It was unveiled by Mr Esmond West, president of the Australian Orthopaedic Association, and was inscribed:

> This plaque was erected in 1952 by the Australian Orthopaedic Association, to commemorate the site of 11 Nelson Street where Hugh Owen Thomas 1834–1891, Robert Jones 1857–1933, T. P. McMurray 1887–1949, practised Orthopaedic Surgery. Their work is immortal



The lintel of Hugh Owen Thomas's surgery door, now displayed in the library of the Medical Institution.

A brief but delightfully interesting address on Hugh Owen Thomas was given by Dr W. Hywel Jones, the author of the play "The Bonesetter of Crosshall Street." Professor Bryan McFarland gave short word-pictures of Robert Jones and McMurray, and Mr West paid a tribute to the Liverpool School in a speech which, like the remarks he has made at various times during his visit to Great Britain, was " just right."

The scene shifted back to the Medical Institution. Mrs McMurray formally opened the door of the Hugh Owen Thomas Library to display the stone which, from 1866 until the blitz in 1941, stood above the lintel of Hugh Owen Thomas's surgery door. It had been rescued from the ruins and carefully preserved. And now in the wall above the library fireplace it was seen for the first time since its original place was destroyed.

ROYAL SOCIETY OF MEDICINE

SECTION OF ORTHOPAEDICS

Admission of Dr M. N. Smith-Petersen to Honorary Membership—At a meeting on June 25, 1952, with Mr Philip Wiles in the Chair, Dr Smith-Petersen of Boston, Massachusetts, was admitted to Honorary Fellowship of the Society by its President, Lord Webb-Johnson, and was given a great ovation.

Lessons learned from fourteen years' experience with mould arthroplasty of the hip joint—Dr Smith-Petersen conceived the purpose of an arthroplasty to be restoration of function by relief of pain and correction of deformity. A mould arthroplasty made it possible to construct the best joint that the available material would allow. If a mechanically perfect joint were fashioned before insertion of the mould, friction and intermittent pressure would clothe the joint surfaces with fibrocartilage over a new subchondral layer of cortical bone. Avoidance of unnecessary resection—"preservation of stock"—would leave something to work upon if secondary operation should prove necessary.

Surgery was justified only by pain, by limitation of activity or by enough deformity to subject other parts to undue strain. The patient must understand the time involved and the limitations expected in the final result. The interposed mould converted a joint of two surfaces into a joint of four surfaces. The approach must adequately expose both surfaces of the original joint. The lower half of the anterior inferior iliac spine and the anterior lip of the acetabulum should be freely removed. The anterior part of the synovial membrane was removed with them; the superior and posterior parts were removed after dislocation. The acetabulum should be deepened to the floor of its notch. Cavities in the femoral neck were curetted to bleeding bone and packed with cancellous chips. Surfaces of raw bone were cauterised, and stability and range of movement were tested before closure. The limb was placed in a Thomas splint and knee-piece. Post-operative treatment should continue for a matter of years.

Failure usually had evident causes, which could often be rectified by an operation for "revision." They included: inadequate removal of exostoses; failure to transplant the greater trochanter when necessary to minimise risk of impingement; inadequate reaming of the acetabulum, so that the articular surfaces remained eccentric (reamers with perforated heads were helpful); use of too small a mould (protrusio acetabuli demanded an outsize); and failure to reattach ilio psoas if the lesser trochanter were removed. Experience had shown the importance of some points of technique: for instance, the lateral cutaneous nerve should be respected; if possible, the origin of gluteus medius should be left intact; the periarticular fat lying in compartments behind iliacus and in front of the capsule provided valuable fields of approach.

Dr Smith-Petersen reviewed the results of primary mould arthroplasties performed on 842 hips in 665 patients, and of 197 "revisions" or secondary operations. One death had been ascribed to operation in the 1,039 cases; there had been forty-two instances of sepsis, but none in the last two years. Secondary operation was called for principally in the "rheumatoid" group.

Election of officers—The officers elected for the 1952–53 season are: President—Mr H. Jackson Burrows (London); Honorary Secretaries—Mr L. W. Plewes (Luton) and Mr H. E. Harding (London).

THE BONE AND TOOTH SOCIETY

A meeting of the Bone and Tooth Society was held on January 10, 1952, at the Institute of Orthopaedics with Mr H. Jackson Burrows in the Chair.

Proposed survey of relationship between bone age and dental age—*Mr G. J. Parfitt* (Institute of Dental Surgery, Eastman Dental Hospital, London) said that in a Home containing 250 children under continual observation by the Ministry of Health Research into Normal Growth, radiographs of the wrist were taken to estimate bone age, and dental examinations were carried out. It was decided to investigate the assessment of age by tooth development. Extra-oral lateral radiographs of the jaws proved practicable. Assessment on the first hundred cases showed that as many as forty observations upon tooth position in eruption and root development could be obtained from some of the radiographs. Sixty per cent of these observations fell between reasonable limits and thereby constituted a method of assessing tooth age. Tooth eruption and root formation were active between the ages of five and twelve; only between these ages was this method valid. Insufficient measurements had been made to assess the variation between tooth and bone age; the investigation would continue for some years.

The nature and development of "enamel" in lower vertebrates—*Dr D. F. G. Poole* (University of Bristol) stated that the teeth and scales of *Rana clavata* have an outer covering layer described by Tomes as specialised and very enamel-like. The physical and optical properties were investigated with the x-ray diffraction techniques of J. Thewlis, and the polarising microscope techniques of W. J. Schmidt. The physical and optical properties of this enamel-like layer of the placoid scale showed remarkable resemblance to those of mammalian enamel and to the enamel-dentine relationship in mammalian teeth. This material was formed by the calcification of an organic matrix produced by the mesodermal odontoblasts, which consisted initially of a mass of fibres running parallel to each other and at right angles to the surface. As calcification proceeded the mineral crystallites became aligned along these fibres, producing a calcified material with

physical properties very like those of mammalian enamel. Eventually the fibres largely disappeared. Evidently, this enamel-like tissue was a specialised part of the dentine papilla, as the ameloblasts played no part in the formation of the original matrix. The enamel-like material of other fish appeared to be formed in a similar way to that of *R. clavata*. Frequently the only covering material the tooth possessed was a layer of hypercalcified dentine, as in *Polypterus*. According to Schmidt, the same is true in certain sharks. Seemingly, therefore, in fish, amphibia, and reptiles the enamel-like material when present was the outer specialised part of the mesodermal dentine papilla, and was not formed in the same way as the ectodermal prismatic enamel of mammals. Kyam had proposed that this tissue be termed *mesodermal enamel* to distinguish it from the ectodermal enamel of mammals.

Variation in organic matter of hard tissues—*Mr M. V. Stack* (Guy's Hospital, London) showed the following table:

PERCENTAGES OF ORGANIC MATTER, ETC.

	Bone	Dentine	Enamel
Organic matter	26–29	19–21	0·4–0·8
Nitrogen . .	4·3–4·9	3·2–3·6	0·03–0·09
Variation . .	3	3	12
Citric acid . .	1·0	0·85	0·10

The Table showed approximate percentages; distributions were somewhat asymmetrical for bone, and normal for the dental tissues. For bone and dentine, similar ratios of nitrogen to organic matter might be calculated. The organic matter in mandibular compact bone was measured at points opposite the teeth which were also analysed to demonstrate variation in enamel and dentine calcification. From comparisons between samples of dentine and enamel from complementary teeth on opposite sides of sixteen dental arches, it was clear that variation in calcification within pairs was of the same order as that among assorted teeth. Nevertheless, some evidence of reduced variability was obtained when examining groups of four symmetrically disposed teeth.

Renal osteodystrophy—*Dr M. D. Milne* (University of Manchester) had studied four cases of renal osteodystrophy, all showing severe osteomalacia with pseudo-fractures (Looser's zones). The cases include two of renal tubular acidosis, one of the Fanconi syndrome and one of classical renal rickets with normotensive uraemia. The essential resemblance between the abnormalities of electroytes in renal tubular acidosis and in the case of the Fanconi syndrome was demonstrated; reasons were given for incriminating the proximal renal tubule in both conditions. Dr Milne ascribed the abnormally high phosphate clearance of these two syndromes, not to a primary renal tubular defect, but to an extra-renal influence—either systemic acidosis or secondary hyperparathyroidism. The results and complications of therapy with alkali, calciferol and calcium lactate (Albright's régime) were discussed.

Bone citric acid—*Dr H. R. Perkins* (Institute of Orthopaedics, London). In view of the comparatively large amount of citric acid in bone (Dickens, Biochemical Journal, 1941, **35,** 1011) and the observation that its presence in solution increases the solubility of bone salt (Kuyper, Journal of Biological Chemistry, 1938, **123,** 405) work has been carried out at the Institute of Orthopaedics on the citric acid cycle enzymes of bone. The kidneys, liver and bone marrow, metaphysis, epiphysial cartilage and diaphysial cortex of young rabbits were employed. It was found that the bone parts contained the enzyme system forming citric acid from oxalo-acetic acid (citrogenase), aconitase and *iso*-citric dehydrogenase. However, whereas the active bone regions contained about one-sixth of the citrogenase activity of kidney, they contained only about one-sixtieth of its *iso*-citric dehydrogenase activity. It thus appeared likely that citric acid formed enzymically might be co-precipitated in the bone salt, the *iso*-citric dehydrogenase present being too little to remove it. Experiments showing that citric acid inhibited the *in vitro* calcification of rachitic cartilage suggested that local citric acid formation might play a part in bone dissolution.

DEMONSTRATION

Focal fibrosis and diffuse fibrosis of bone—*Mr E. D. D. Davis* (London) showed plaster models, radiographs and microscope slides of cases of focal fibrosis or fibrous dysplasia of the

maxilla. These cases were a selection made from thirty-two cases of focal fibrosis seen during about thirty years. Five patients with focal fibrosis developed well marked leontiasis ossea (diffuse fibrosis), one of which exhibited focal fibrosis of the lower end of the humerus. Paget's osteitis deformans occurred in three patients. The microscope slides were made from patients aged twelve, twenty and forty-five, all with focal fibrosis of the maxilla. The sections showed more bone formation, less giant cells and less fibrous tissue as the patient grew older. The oldest patient had extensive leontiasis ossea with involvement of the spine. A few radiographs and sections of circumscribed fibromata and ossified fibromata of the mandible and maxilla were shown in contrast to the cases of focal fibrosis.

SYMPOSIUM ON CALCIFICATION IN STRUCTURES OTHER THAN BONE

A further meeting was held at the Institute of Orthopaedics on March 31, 1952, with Professor W. D. Newcomb in the Chair. Calcification in structures other than bone was discussed.

Shell regeneration in helix aspersa—*Dr L. E. Wagge* said that rapid repair of the shell in helix aspersa and many other land molluscs was effected by amoebocytic action. Calcium carbonate and proteins were carried by amoebocytes to the damaged area from reserves either in the digestive gland or in the shell. Alkaline phosphatases were abundant during shell repair, especially about the lining cells of the digestive gland, and probably played an important role in calcification. Digestion and shell repair were closely associated: a starved snail could not use reserves efficiently. Attempts to study the role of vitamin D in calcification in the snail were inconclusive, because no adequate synthetic diet was available, and because precise quantitative analysis was prevented by variability in molluscular vital processes, especially those connected with concentrations of body fluids. Dr Wagge then discussed differences between shell repair and shell formation in the snail.

The orientation of calcareous spicules in sponges—*Mr W. C. Jones* said that calcareous sponges possessed a skeleton of crystalline units ("spicules") of which one type had three rays and was embedded in the layer of jelly in the wall of the sponge. In leucosolenia this type tended to be set with one of the rays pointing to the base of the sponge tube; the crystalline substance (calcite) was also orientated, the optical axis lying in an axial plane of the tube and inclining towards the tube apex. Each spicule was formed by a sextet of three pairs of cells which first secreted a three-rayed organic precursor upon which the calcite subsequently crystallised. Preliminary experiments (reversal of water flow through sponge tubes and the stretching of isolated pieces of wall) yielded patterns of young triradiates which suggested that their orientation was due to a displacement of the layers of the wall relative to one another. This led to the following hypothesis: the sextets are anchored to the inner cell-layer and are appropriately rotated and tilted by the surrounding jelly, which flows from the basal (feeding) zone of the tube, where it is secreted, into the apical growing regions; the tilting of the trigonal symmetry axis of the sextet results in the inclination of the spicule optical axis since the two axes coincide through the "orientated overgrowth" of the calcite upon the organic precursor. The hypothesis had been partly verified by histological evidence of the arrangement of the sextets, and by the photographic recording of spatial changes occurring during the development of the tube.

Egg shell formation in birds—*Professor C. Tyler* stated that, before and during laying, calcium absorption from the food was increased, and hormones produced changes in the blood and in the structure of the bones, so that the shell gland was supplied with calcium partly from the food and partly from the bone, and heavy excretion of phosphorus was observed with each egg laid. Mechanical stimulation caused secretion of shell material. Calcium came from the reservoir of non-diffusible calcium in the blood, and carbonate was produced by the carbonic anhydrase system. Precipitation then occurred on the egg membrane because of pH differences. The rate of formation, after a slow start, was constant. Shell structure was as follows: a layer of nodules next to the membrane; then a mass of unorientated crystals; and finally orientated crystals on the outside. The shell was penetrated by pores plugged with protein. The shell was composed chiefly of calcium carbonate cemented together by protein with magnesium and phosphorus in small amounts.

Pathological calcification—*Dr J. W. Landells* said that physico-chemical considerations suggested that the blood was nearly, if not actually, supersaturated with calcium and phosphate ions, and it was hardly surprising that calcium deposits were common in pathology. Two distinct types occurred: *metastatic*, in which the blood chemistry was abnormal; and *dystrophic*, in which the cells were abnormal and usually dead or dying but the blood chemistry was normal. Rarer examples were known in which neither blood nor cell was obviously deranged. Metastatic deposits were no mere random precipitation, but their site, their form and their chemistry were particular; and they were the same however the abnormal blood chemistry had been brought about. The composition, as far as was known, resembled the mineral of bone, and attachment to collagen

membranes emphasised the similarity. Dystrophic calcification was even less well worked out. Even though the chemistry was not known, there too the absorption of calcium was attended by changes in the matrix which persisted after the calcium was removed. Probably the first step was a change that provided a point for calcium deposition, rather than a humeral change leading to precipitation in the fluids of the part. The subsequent accretion to visible dimensions was likely to follow chemical and crystallographic laws. In rarer cases, calcium was deposited by a chemical change in substances already formed by the body cells between them. Calculus formation outside the body, in cavities such as the renal tubules or gall bladder, was not considered.

VITAMIN A AND BONES AND TEETH

A further symposium was held at the Institute of Orthopaedics on June 26, 1952, with Sir Edward Mellanby in the Chair. *Sir Edward Mellanby*, introducing the discussion, said that the first indication that vitamin A was concerned with bone structure came when Collago and Rodriquez in 1933 described fractures in the long bones of young rats caused by hypervitaminosis A. Histological changes of the fragile bones were described by Strauss (Beiträge zur pathologischen Anatomie und zur allgemeinen Pathologie, 1934, **94,** 345), and by Wolbach and Bessey (Physiological Reviews, 1942, **22,** 233). Maturation and degeneration of cartilage cells and replacement of cartilage by bone were greatly accelerated, with early closure of epiphyses and loss of previously formed cortical bone. Mellanby's experiments made to find an explanation why young vitamin-A-deficient animals developed widespread degenerative changes of central and peripheral nerves, with deafness and inco-ordination of movement, showed destruction of both divisions of the eighth cranial nerve by bony overgrowth of the internal auditory meatus. This started an investigation which showed that most of the nerve degenerative changes of vitamin-deficient animals could be explained directly or indirectly by periosteal bone overgrowth. The essential point was that where bone cavities, such as the spinal canal or internal auditory meatus, ought to have expanded to make room for the growing nervous tissue, they contracted because new bone was laid down rather than removed. Closer histological examination revealed that in hypovitaminosis A the osteoclasts and osteoblasts changed their normal orientation with subsequent development of new bone shapes. Changes differed in different bones. Sometimes, for instance in the internal auditory meatus and the spinal canal, there was reversal of position and activity, excessive bone being laid down where it ought to have been removed. At other places, for instance the sphenoid bone or the orbital canal, changes were more complicated. The change in any particular bone in vitamin A lack were determined by the normal pattern of growth at such a point. It was often possible to determine the normal manner of even complicated growth by adding vitamin A to the diets of deficient animals. There was then a reversal to the normal arrangement of cells, but the response was excessive, as if Nature were making a great effort to remould the bones to their normal shape before growth ceased. In vitamin A deficiency, bones became thicker and coarser. The new periosteal bone was more cancellous. There was no alteration in the total calcium of a bone, but it was more scattered in the hypertrophied cancellous bone. Wolbach had described changes in rat epiphysial cartilage growth on vitamin-A-deficient diets, and concluded that vitamin A controls the sequence of changes. The speaker had never seen these changes in puppy cartilage, but working with very young rats deficient in vitamin A, he had confirmed Wolbach's result. It seemed impossible at present to formulate any generalisation which will account for all these effects.

The effect of vitamin A on skeletal tissue in culture—*Dr H. B. Fell* described work done in conjunction with *Sir Edward Mellanby* on the effect of excessive vitamin A on the differentiation of early long-bone rudiments. Limb cartilages from six-day chick embryos were cultivated *in vitro* in media containing excess of vitamin A and in control media. The controls in normal medium elongated rapidly, the cartilage differentiated as *in vivo* and a layer of periosteal bone was deposited. In medium containing excess vitamin A, elongation was arrested but the cartilage differentiated at the normal rate into its characteristic cellular zones, and ossification was only slightly reduced. The cartilage matrix, however, was greatly affected: it shrank, softened, lost its basophilia and metachromasia but stained much more intensely with van Gieson's stain; these changes were not associated with cell degeneration, and the soft tissue grew vigorously. The effect of excess vitamin A on well developed bones was studied in the explanted limb bones of mouse foetuses near term. The cartilage matrix rapidly dwindled, lost its metachromasia and finally disappeared leaving the chondroblasts naked; the bone became rarified and eventually was almost completely destroyed. Heating the bones to 45 degrees centigrade prevented both their growth in normal medium and their reaction to excess vitamin A. The effect on the explants of plasma from a fowl with hypervitaminosis A was like, but less than, that of normal plasma containing the same amount of vitamin A added artificially. The nature of the effect of hypervitaminosis A on the skeleton

should be considered in relation to its action on other tissues. Recent experiments had shown that excess vitamin A completely inhibited keratinisation in explants of epidermis from six-to-seven-day chick embryos and transformed the epithelium into a mucus-secreting membrane in which ciliating cells were often seen; this effect was reversible. Controls in normal medium formed only keratinising, squamous epithelium.

The biochemical effects of vitamin A—*Dr T. Moore's* communication, in his absence, was read jointly by Dr Sharman and Mr Ward. They showed that the biochemistry of vitamin A had been most successfully studied in the rhodospin system of the retina, but there was no evidence of the existence of this system in other parts of the body. When animals were deficient in vitamin A the ability of membranes to secrete mucus was suppressed, which suggested that the vitamin might be concerned in the formation of glyco-proteins. In the bones the balance between the formation of collagen and chondroitin sulphuric acid might possibly have been affected by the vitamin. The action of vitamin A on the vaginal epithelium appeared to be opposed to that of oestradiol, and it would be interesting to seek evidence of a similar opposition in the formation of bones and teeth. Evidence of the intervention of the vitamin in general protein metabolism was found in the ability of the vitamin to increase the resistance of rats to diets low in protein and also to poisons which required products of protein metabolism for their detoxication. Although the evidence of the effect of excess of vitamin A on cultured bone suggested that it had a direct action on the tissues, there was some evidence for an indirect action. Thus in normally nourished animals vitamin A was not readily demonstrable by chemical means in tissues that were highly vulnerable to its absence. Vitamin A activity, moreover, may have been detected biologically in materials, such as lard distillate and synthetic vitamin-A acid, which did not give the chemical tests for vitamin A. The bleached enamel of the incisor teeth of rats deficient in vitamin A contained less iron than did normal enamel. In Britain, as earlier reported from America, blindness has been caused in calves fed mainly upon sugar-beet pulp, through malformation of the skull and injury to the optic nerve. In the speakers' own experiments areas of rarefaction were noticed in the bones of a rat which had been exposed to combined partial deficiencies of vitamin A and protein. The great enlargement of the lymph glands in the neck and elsewhere and the increased size of the spleen suggested that the skeletal lesions were secondary to a condition resembling human leukaemia.

Vitamin A and bones and teeth—*Dr N. A. Barnicot* described work carried out in collaboration with *Dr S. P. Datta* which included bone lesions produced in rats on high dosage of vitamin A. He also showed that local implants of vitamin A produced well marked resorption, accompanied by numerous osteoclasts, leading to perforation of parietal bone grafts inserted into cerebral hemispheres of litter-mate mice.

The effects of vitamin A deficiency on the teeth and jaws of experimental animals—*Dr J. D. King* showed that, in dogs and rats, vitamin-A deficiency during development led to hyperplasia of the gum epithelia, with subsequent parodontal disease, to degeneration of the afferent dental nerves, to retarded tooth growth, to hypoplasia of enamel and dentine, and to abnormal deposition of cementum and alveolar bone. The bony and cemental changes caused compression of the dental nerves and vessels, which might in turn have accounted for the epithelial lesions and growth inhibition. In the molar regions of vitamin-A-deficient rats keratinisation of the parodontal pocket epithelium facilitated formation of dental calculus (tartar).

HONOUR TO ORTHOPAEDIC SURGEON

MR S. A. S. MALKIN

We are pleased to report that Mr Alan Malkin has received the distinction of the C.B.E. after many years in Nottingham, where he has been largely instrumental in creating an orthopaedic service with its central hospital at Harlow Wood and an independent training college for the disabled.

Qualifying from University College Hospital, London, in 1915, Malkin at once joined the R.A.M.C. and served as a regimental medical officer, being twice mentioned in despatches. At the end of the war he joined those who were being trained in military orthopaedics to replace Americans who were returning home. He spent twelve months at the Special Military Surgical Hospital, Hollymoor, Birmingham, under Naughton Dunn and, on return to civil life, held a series of resident posts at the West London Hospital, before becoming House Surgeon at the Royal National Orthopaedic Hospital and later Clinical Assistant at St Bartholomew's and at the Children's Hospital, Great Ormond Street. Later he held the post of Resident Surgical Officer at what is now the Royal Orthopaedic Hospital, Birmingham.

In 1923 he was appointed Surgeon to the Nottingham Cripples Guild with the object of developing the national plan of Sir Robert Jones for the prevention, treatment and training of

cripples. At first practically no facilities were available except a very small clinic and a few beds lent by Naughton Dunn at the Warwickshire Orthopaedic Hospital for Children, Coleshill. He was fortunate in finding as President of the Nottingham Cripples Guild Winifred, Duchess of Portland, who was keenly interested in the welfare of cripples. With her enthusiastic support, the public conscience was aroused and orthopaedic clinics were established in various parts of Nottinghamshire. In 1929, with the help of the first Lord Trent and many others, Harlow Wood Orthopaedic Hospital was built on land given by the Duke of Portland. This was gradually enlarged; and, during the second world war, comprised, with various annexes and a rehabilitation centre, about 600 beds. At present the hospital has 330 beds and serves the East Midlands for long-stay patients besides providing an accident service for a more restricted area.

After the second world war, a committee was formed with the object of creating a College; and in the last few years more than £130,000 has been raised by voluntary effort. In 1949 the foundation stone of the Portland Training College was laid by the present Queen; and in 1950 the College was opened by Elizabeth the Queen Mother. It collaborates closely with the Ministry of Labour, which makes maintenance grants, but the management is purely voluntary. Malkin took a leading part in stimulating public opinion and in raising funds, and he is Vice-Chairman of the College. Thus a plan, begun in his early days, has been brought to fruition.

BRITISH ORTHOPAEDIC ASSOCIATION

ROBERT JONES GOLF CUP

The annual competition for the Robert Jones Golf Cup was held on July 1, 1952, at Sunningdale, during the combined meeting of the orthopaedic associations of the English-speaking world. For the first time members of overseas orthopaedic associations were invited to take part and the home players were delighted that so many visitors were able to play. The record entry of thirty-two competitors included representatives from all parts of the English-speaking world, who will always remember a most enjoyable afternoon spent in typically English surroundings. The day was cloudless and hot—in fact rather too hot; but Sunningdale was green and its glorious trees did their best to provide some shade.

The Cup, which is dedicated to the memory of Sir Robert Jones, was won by Dr A. S. McConkey of Vancouver, who returned the excellent score of 83—14=69. Mr G. K. McKee of Norwich was second with a net 70. At the Annual Dinner later in the week the Cup was presented to the winner by Mrs Rowley Bristow.

BELGIUM

BELGIAN SOCIETY OF ORTHOPAEDICS AND OF THE SURGERY OF THE MOTOR SYSTEM

Thanks to the energy and perseverence of Dr Paul Lorthioir, the Société Belge d'Orthopédie et de Chirurgie de l'Appareil Moteur has been one of the most active scientific societies in Europe over the last twenty-five years. Its members, together with visiting colleagues from Holland and Northern France, meet every month. The Committee for 1951–52 includes the president, Dr Marcel Soeur of Charleroi, the vice-presidents, Dr P. Marique of Brussels and Dr H. Bonet of Liége, and the general secretary, Dr Fernand Poncelet, 62 Avenue de la Toison d'Or, Brussels.

The papers presented to the Society are published in French every month in its official journal, *Acta Orthopaedica Belgica*. Each year the society discusses one particular subject in detail and this year Drs Robert Soeur, E. Berckmans, J. Simonart and Ch. De Racker presented a symposium on the pathogenesis and classification of osteochondritis.

DEVELOPMENTS IN ORTHOPAEDIC AND ACCIDENT SURGERY

Belgium does not possess any large institutions specially reserved for orthopaedic surgery although with government aid most cases of tuberculosis of bone are taken care of either in the clinic of Dr Delchef at Neeryssche in the open country near Brussels or on the Belgian coast in the Institut Hélio-marin at Le Coq near Ostend under the care of Dr Blankoff and Dr Fernand Parisel. (Incidentally, Dr Blankoff frequently contributes most interesting reviews of Russian orthopaedic work to the Acta Orthopaedica Belgica.) Although most patients with poliomyelitis are still being looked after by individual physicians, perhaps the most active worker in this direction is Dr Laruelle of Brussels.

The heavy industry of the coal mines and steel manufacturing of Belgium provides large numbers of industrial accidents. Two of the main centres dealing with traumatic surgery are located in Brussels with Dr Bélenger as director, and in Charleroi under the direction of Dr Desenfans.

The four Universities of Belgium—at Brussels, Louvain, Ghent and Liége—all possess medical faculties. There is, however, comparatively little organised teaching of orthopaedics, although Professor Jean Verbrugge has recently been appointed by the Government to the Chair of Orthopaedic Surgery in the University of Ghent. It is the hope and aim of many active workers in this field that teaching of the subject should be made compulsory in the four universities and that ultimately a higher diploma should be instituted.

WEST AFRICA

ORTHOPAEDIC SURGERY IN NIGERIA

Mr A. F. Bryson, lately of Manchester, England, has been appointed Senior Orthopaedic Specialist, Nigeria, under the auspices of the Colonial Service. He has already left to start an orthopaedic service at Kano in Northern Nigeria.

INDIA

ALL-INDIA CONFERENCE ON POLIOMYELITIS AND REHABILITATION OF CRIPPLES

The All-India Conference on Poliomyelitis and Rehabilitation of Cripples, which was due to be held in December, 1952, as announced in the May, 1952, issue of the Journal, has been postponed until December 1953. Precise dates will be announced later.

INTERNATIONAL SOCIETIES

INTERNATIONAL SOCIETY OF ORTHOPAEDIC SURGERY AND TRAUMATOLOGY

The Sixth Congress of the International Society of Orthopaedic Surgery and Traumatology will be held in Berne from September 6 to 10, 1954, under the presidency of Professor Etienne Sorrel of Paris. The scientific programme will consist of a symposium on two main subjects, short papers and clinical and operation demonstrations in the leading Swiss hospital centres. The two chief subjects chosen for discussion are: Scoliosis, to be opened by Professor Bryan McFarland of Liverpool, with the collaboration of Mr J. I. P. James of London; and The Surgery of the Hand, to be opened by Professor Robert Merle D'Aubigné of Paris.

Book Reviews

TECHNIQUES IN BRITISH SURGERY. Edited by Rodney Maingot, F.R.C.S., Surgeon, Royal Free Hospital, London, and Senior Surgeon, Southend General Hospital. 10×6¼ in. Pp. xx + 733, with 473 figures. Index. 1950. Philadelphia and London: W. B. Saunders Company. Price 75s.

This excellent book contains thirty-two essays on selected aspects of surgery, and, as the editor modestly hopes, it does give a truly liberal cross-section of current British surgical practice. Mr Maingot, whose own writing is limited to a short preface, has wisely chosen contributors who are both active surgeons and good teachers; the result after careful production is a book that is a pleasure to read. The fourth part, consisting of eight chapters on the surgery of the extremities, holds most interest for orthopaedic surgeons. The reviews of recurrent dislocation of the shoulder, by Crawford Adams, and of nerve suture, by Zachary, may perhaps be mentioned specially for the amount of well-balanced information they give, each in the compass of sixteen pages. Denis Browne's contributions on congenital dislocation of the hip and on talipes are thoroughly personal. He begins with the words "I assume," and here the publisher's peculiar habit of having the first letter of each chapter an inch high seems to stress the point. The set-backs of congenital dislocation are lightly dismissed in four lines, and the only treatment mentioned for relapsed or neglected cases of talipes is manipulation with the powerful calcaneus wrench. The remaining four essays, on arthroplasty by Vaughan-Jackson, on bone transplants by Dick, on infections of the hand by Professor F. H. Bentley and on the management of gangrene by Professor A. M. Boyd, maintain the general high standard of text and illustration. The reader pleasantly browsing elsewhere will come across a chapter on congenital defects of the heart by Professor Walter Mercer which must excite admiration of his wide surgical interests. The editor and the American publisher are to be congratulated upon the way these thirty-two fascinating essays have been collated and presented.—K. I. Nissen.

THE SCIENCE AND ART OF JOINT MANIPULATION. By James Mennell, M.A., M.D. Consulting Physician in Physical Medicine, St Thomas's Hospital. Volume II—The Spinal Column. 10×7½ in. Pp. vii + 264, with 148 figures. Index. 1952. London: J. & A. Churchill Ltd. Price 42s.

The second edition of joint manipulation of the extremities was published in 1949, when Dr James Mennell was much occupied in California. The hard work of preparation of the second volume, which concerns the spinal column, was completed in Hampshire and is the subject of this review. Like the first volume, this is a record of the thoughts, experience and teaching of the author. The title is rather a misnomer, for the subject matter is, first, largely the study of the anatomy and physiology of interest to the exponents of orthopaedic surgery and physical medicine, and secondly, the symptomatology, diagnosis and non-operative treatment of backache. The casual reader, who may think he is going to find a description of the treatment of a prolapsed intervertebral disc by manipulation, must look elsewhere, but he will be repaid by reading this book from cover to cover. Part is a revision of the author's monograph on backache, and he makes no claim that this book is a complete and up-to-date treatise on every aspect of trouble in the back. There is information, gained from personal observation and records, that is of great interest; but science advances with such strides that the complete study of this subject can hardly be recorded now by a Physician in Physical Medicine. The work in the laboratory and orthopaedic wards and theatres is complementary and little recorded in this volume. In fact, credit is given to the original teachers and little to the present-day workers who have sufficient data to assess non-operative, manipulative and operative treatment for various lesions of the back. The author has just written his experience in his own honest way in the hope it will help others, both patients and doctors. He writes as if he does not mind if no one agrees with his views, which are arrived at after very careful experience and consideration and are pleasantly controversial. Observations on the unusual, such as the "pyriformis syndrome," will interest many.

The outstanding sections of the book are those on clinical examination and manipulation, which are made particularly helpful by the two-colour line drawings. Together they represent less than half the book, but are presented excellently for study and adoption. They represent a record of part of the life's work of a great thinker. Some remarks on spina bifida, unusual lumbo-sacral joints, spondylolisthesis and coccydinia may be controversial, but it would be difficult to criticise the account of sacro-iliac lesions, which is the record of forty years' experience. Interest in the intervertebral disc is now international, and it is puzzling that the author has given us little information. One looked in vain when manipulation was likely to help if there was nerve root irritation, and when it was liable to aggravate the symptoms, and what could be learnt by the

FIG. 112

onset of aggravation. Attention is given to "fibrositic deposits," but in the author's experience they do not appear to be of particular interest or importance, nor does he record how frequently they are found in routine examination of the back. He does not draw attention to work on them and he offers no explanation of their cause, which might be more convincing than the popular ones of the day.

Everyone engaged in physical medicine and orthopaedic surgery should study this book. It will interest many others, particularly those impressed by Dr Mennell's demonstrations. He teaches nothing dramatic, but the subject is a difficult one to describe by writing and difficult to learn from a book. The illustrations enable readers to understand the context easily. Readers of English are the richer for this excellent publication by J. & A. Churchill.—St J. D. BUXTON.

PROGRESSIVE RESISTANCE EXERCISE. Technic and Medical Application. By Thomas L. DELORME, M.D., Assistant in Physical Medicine, Massachusetts General Hospital, and Arthur L. WATKINS, M.D., Assistant Clinical Professor of Medicine, Harvard Medical School. 9¼ × 6 in. Pp. xi + 245, with 89 figures and 13 tables. Index. 1951. New York: Appleton-Century-Crofts Inc. Price $5.00.

It is a well established clinical observation that muscle tissue hypertrophies in response to repeated exercise against a gradually increasing load. The most striking examples of this are seen in unstripped muscle, for instance the colon in chronic intestinal obstruction, the bladder in prostatic enlargement, or the left ventricle in hypertension. But the same principle holds good in skeletal muscle, provided the resistance increases gradually enough and the muscle exercises against it often enough, a fact that professional weight lifters have used for a long time as the basis of their training. The authors of this small book have applied it to the redevelopment of power in muscles weakened by injury or disease and they describe the apparatus and technique

elaborated for this purpose in their clinics. There have been misgivings on the part of many competent observers because it has been found that resistance exercises can be harmful as well as beneficial. The authors are aware of the danger of producing sprains and joint effusions by faulty technique and have devised their methods accordingly.

In the past, orthopaedic surgeons have perhaps thought too much in terms of *range* of movement, particularly after fractures, and not enough in terms of power. (It is worth while remembering that the extreme example of range without power is a flail joint.) Nowadays there is a welcome tendency to recognise the importance of power in muscle, and any system of exercises that aims at developing this deserves the careful study of the orthopaedic surgeon. This book will also be of interest to physical medicine specialists, physiotherapists and remedial gymnasts.—E. A. Nicoll.

BONE LESIONS OF YAWS IN UGANDA. By C. J. Hackett, M.D., F.R.C.P. Director, Wellcome Museum of Medical Science, London. 10 × 7½ in. Pp. 194, with 133 figures. Index. 1951. Oxford: Blackwell Scientific Publications. Price 45s.

Like syphilis, yaws is caused by a spirochete and has primary, secondary and tertiary manifestations. The Kahn test is positive, the lesions respond to neoarsphenamine and the bone lesions mimic those of syphilis. Is it then a separate disease? Probably yes, for in the Lango district of Uganda syphilis is an uncommon disease, accounting for only 1 per cent of out-patients, whereas yaws accounts for 20 per cent of out-patients.

Hackett in the course of two six-month visits to Lango saw 362 cases of yaws with bone lesions. In the secondary stage the characteristic changes were periosteal new bone and cortical rarefactions. All these tended to disappear spontaneously, leaving perhaps some thickening of bone. In the tertiary stage the common appearance was a number of rarefied areas in the medulla and thickening of the cortex. Similar lesions are seen in syphilis, and it is difficult or impossible on radiological evidence to distinguish the two diseases. This authoritative monograph is welcome, not least for the clarity of its illustrations. The numerous radiographs give a clear picture of the bone lesions found in yaws.—George Perkins.

SCOLIOSIS, PATHOLOGY, ETIOLOGY AND TREATMENT. By Samuel Kleinberg, M.D. Attending Orthopaedic Surgeon, Hospital for Joint Diseases; Consulting Orthopaedic Surgeon, Lebanon Hospital, Maimonides Hospital, Hospital for Special Surgery, New York City. 9 × 6½ in. Pp. xv + 286, with 163 figures. Index. 1951. London: Baillière, Tindall & Cox. Price 57s. 6d.

Some twenty-five years ago Dr Kleinberg wrote an excellent monograph on scoliosis. It has now been revised, or, it would be more accurate to say, rewritten. He has even managed to reduce its size considerably, a most meritorious and unusual feat. A comparison of the two editions suggests that little has changed in the surgery of scoliosis, whereas the last twenty-five years have seen some notable advances. Dr Kleinberg does not believe that measurement of curves is of value, yet it is this objective method which has enabled us to discard many of the older ideas which still find a place in this book. It is indeed an excellent review of scoliosis but some modern concepts are not expounded. Dr Kleinberg may not agree with them but it would have been an advantage to have discussed them more fully. Despite this criticism the orthopaedic surgeon interested in scoliosis should not fail to read this small volume.—J. I. P. James.

ARCHITECTURAL PRINCIPLES IN ARTHRODESIS. By H. A. Brittain, O.B.E., M.A., M.Ch., F.R.C.S. Director of Orthopaedic Services, Norfolk and Norwich Group of Hospitals. With a Foreword by Sir Harry Platt, M.D., M.S., F.R.C.S., F.A.C.S. (Hon.). Second edition. 9½ × 7 in. Pp. xi + 196, with 257 figures, 9 in colour. Index. 1952. Edinburgh and London: E. & S. Livingstone Ltd. Price 42s.

Mr Brittain's second edition has appeared ten years after his first, and the experience of those years has reinforced his original views about arthrodesis and about its underlying principles. It is not for a reviewer of his second edition to question whether or not these principles are truly "architectural," and the point is surely one of little importance for the soundness of their biological physics is, after all, what really matters. The temptation to make this book into an encyclopaedia

of arthrodesis has been avoided. In the main it still deals only with those techniques which have come from the fertile brain of its author and, though he has included new material in nearly every part of the book and though much of this new material consists of illustrations, he is to be congratulated on his success in enlarging the volume by no more than one-third. Ischio-femoral arthrodesis, now an accepted and standard operation, is described with very little alteration from the account given in the first edition. A vast experience of the procedure has confirmed Mr Brittain's preference for a blind lateral approach. He is able to dismiss all alleged drawbacks and hazards of that approach on the grounds that none of the reported mishaps have occurred in any of his own 154 operations. The modified ischio-femoral fusion which he terms "V-arthrodesis" receives its definitive description in this volume, and there are new chapters on arthrodesis of the symphysis pubis and of the carpo-metacarpal joint of the thumb. The original operation for fusion of the wrist has undergone an important modification in that the bail graft is now supported by two other grafts at its weakest point. As an appendix Mr Brittain gives us a well illustrated account of the classical Naughton Dunn operation for stabilisation of the foot. Purists may point out that the skin incision is not quite the one used by Dunn himself and, no doubt, other quibbles about minor details may be justified, but it is very good to have this account of a standard operation which has never before been so adequately described and illustrated. The book is of the usual standard achieved by its publishers. The illustrations, new and old, are very good indeed.—D. Ll. Griffiths.

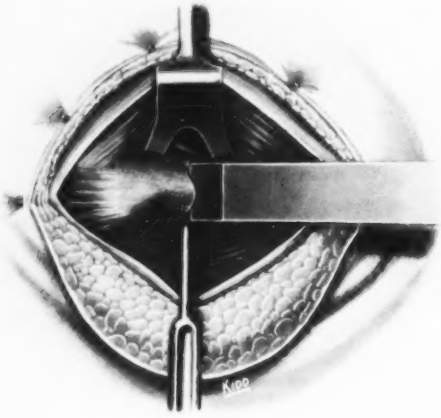


Fig. 40

Avoiding the sciatic nerve

If the posterior edge of the chisel is above the posterior margin of the great trochanter and the chisel is maintained horizontally the sciatic nerve cannot be encountered.

FRACTURES AND ORTHOPAEDIC SURGERY FOR NURSES AND PHYSIOTHERAPISTS. By Arthur Naylor, Ch.M., M.Sc., F.R.C.S. (Eng.), F.R.C.S. (Ed.). Consultant in Orthopaedic Surgery, Bradford Royal Infirmary. Foreword by Professor Sir Ernest Finch, M.D., M.S. (Lond.), F.R.C.S. (Eng.). Third edition. Pp. xv + 315, with 254 figures. 9 × 5½ in. 1952. Edinburgh and London: E. & S. Livingstone Ltd. Price 22s. 6d.

The third edition of this book has been carefully revised, particularly with regard to the illustrations, which now reach a high average standard. The text imparts a wealth of that basic information which is so necessary both for intelligent orthopaedic nursing—whether in the wards, the operating theatre or the out-patient clinic—and for effective physiotherapy. The diagrams and radiographs show a steady improvement in successive editions. It is quite a relief to find Böhler's iron omitted in favour of a walking rocker. It might, however, be fair to comment that it is difficult for a nurse to appreciate a page of diagrams showing the early and late stages of deformity of a tuberculous hip; that new radiographs of calcified deposits in the supraspinatus tendon and of myositis ossificans should be found clear enough not to require arrows; and that the films of congenital dislocation of the hip, Perthes' disease, Freiberg's infraction and march fracture are of poor quality. The diagram of spike arthrodesis of a hammer toe shows the proximal phalanx whittled down to a very sharp point; such a spike of concellous bone almost invariably breaks off at some stage of the operation. Purgation is not generally accepted as part of the routine treatment of periarthritis of the shoulder joint. Such minor criticisms detract very slightly from the practical value of a book which otherwise is being kept well up to date.—K. I. Nissen.

BOOKS RECEIVED

These books are acknowledged with grateful thanks. Selections will be made for review as space permits and in accordance with their interest for our readers.

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Acta Chirurgiae Orthopaedicae et Traumatologiae Cechoslovaca
Acta Chirurgica Scandinavica, and Supplements
Acta Orthopaedica Scandinavica
Annals of the Royal College of Surgeons of England
Archives of Surgery
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Australian and New Zealand Journal of Surgery
Boletin de la Sociedad de Cirugia del Uruguay
British Journal of Surgery
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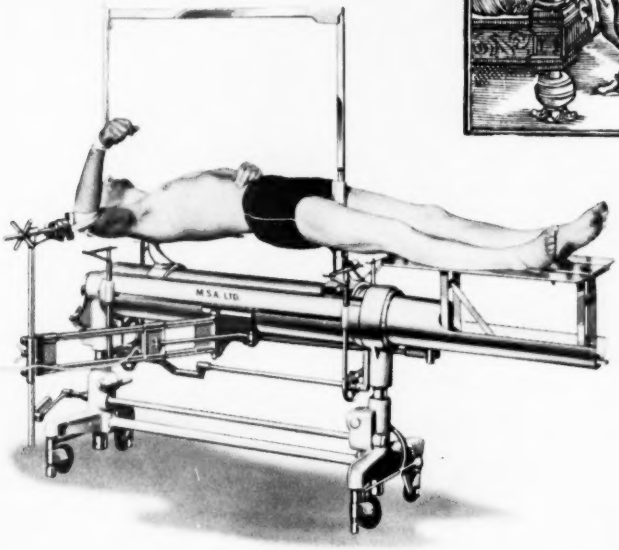

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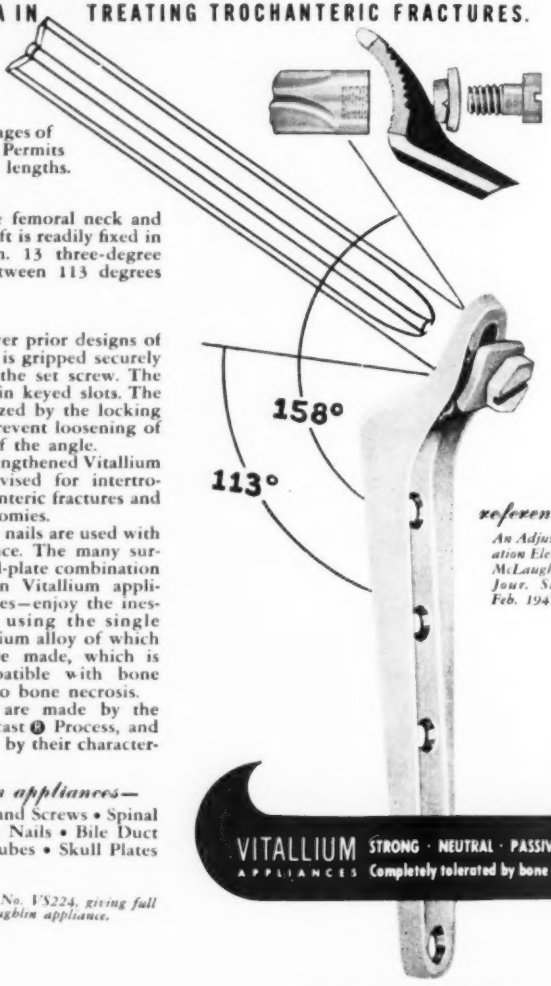

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An Adjustable Internal Fixation Element for the Hip—McLaughlin, H. L., Amer. Jour. Surg. LXXIII-2, Feb. 1947.

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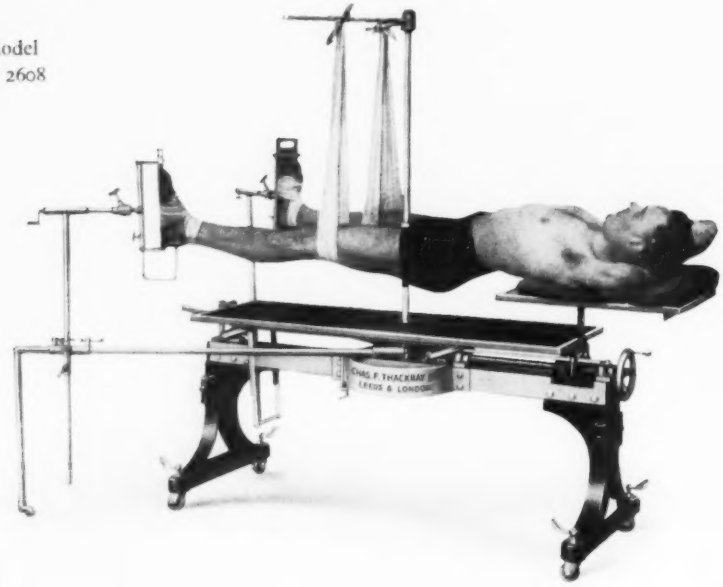

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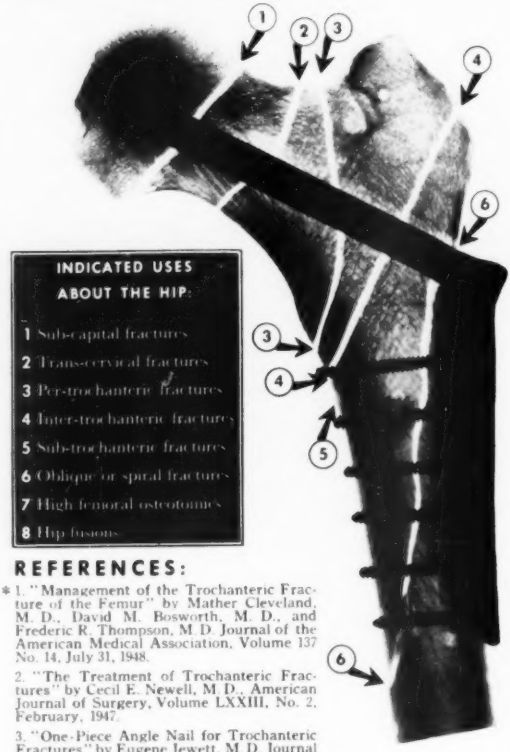

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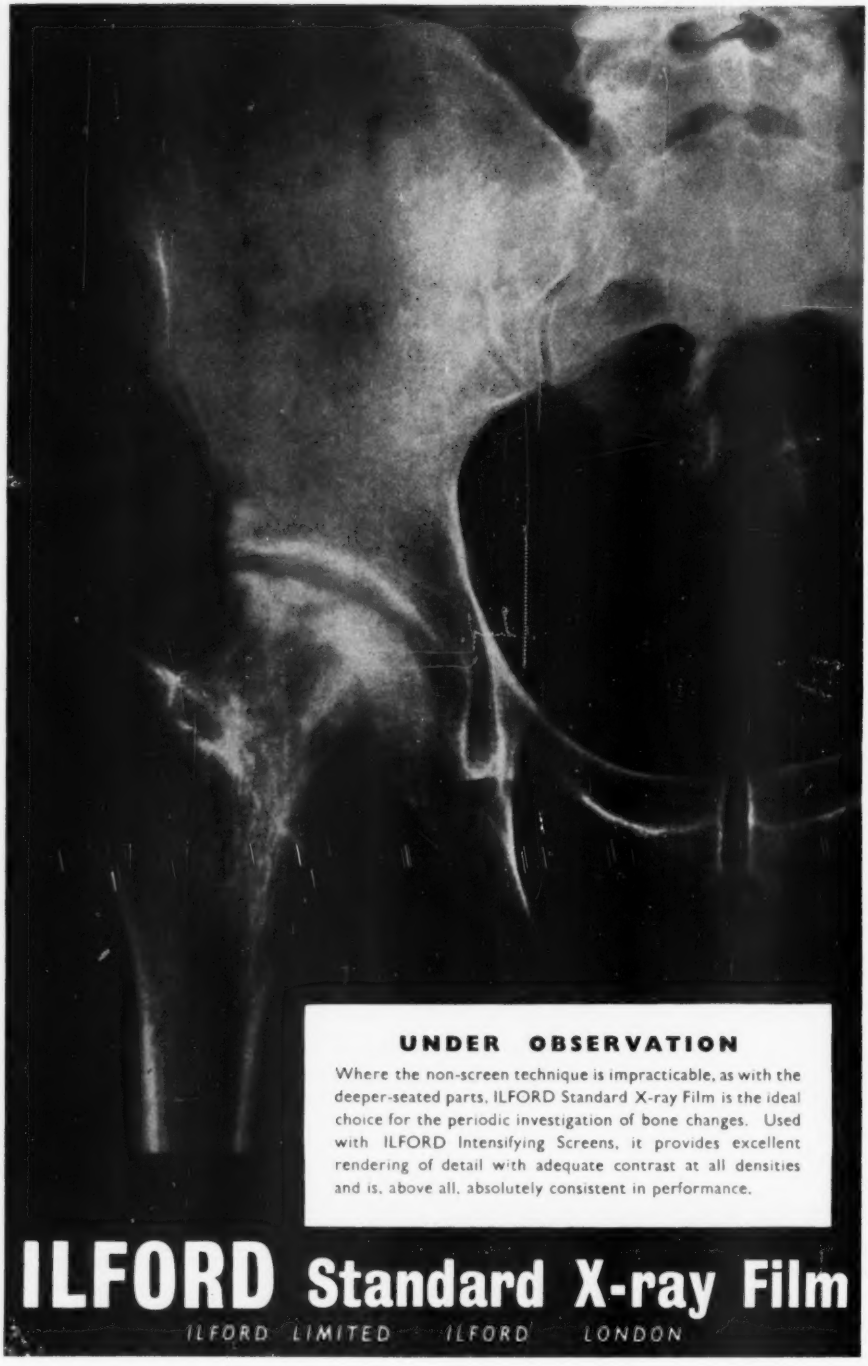
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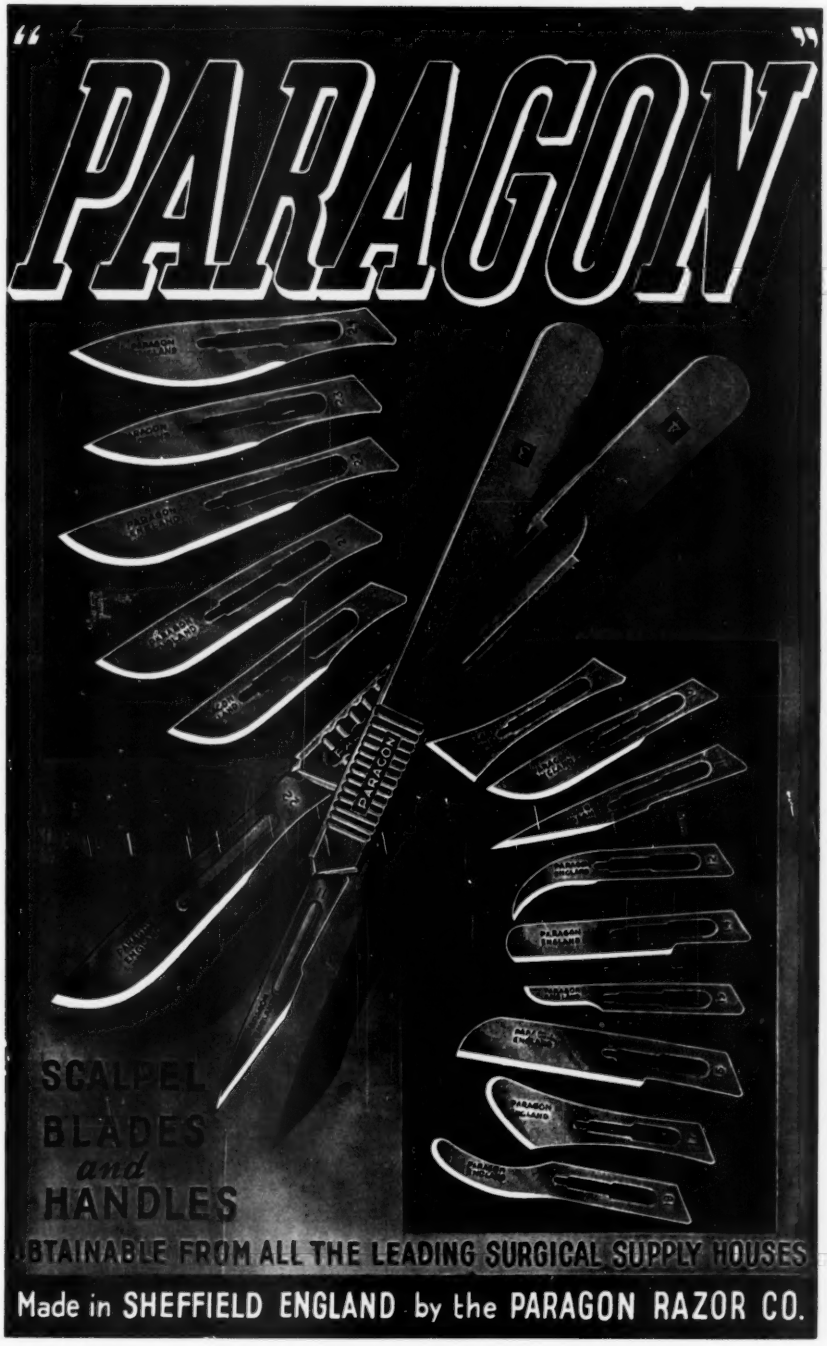
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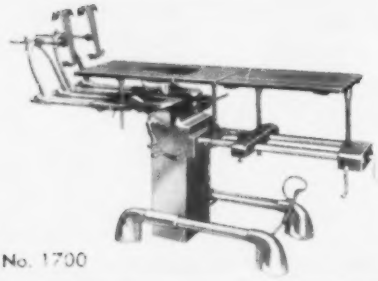

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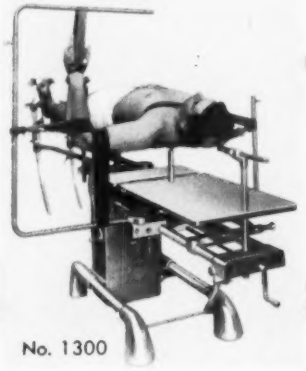

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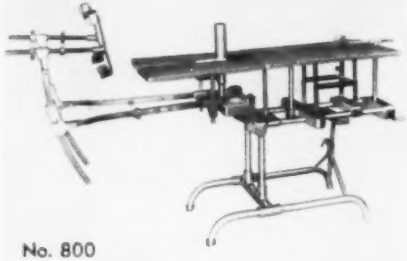

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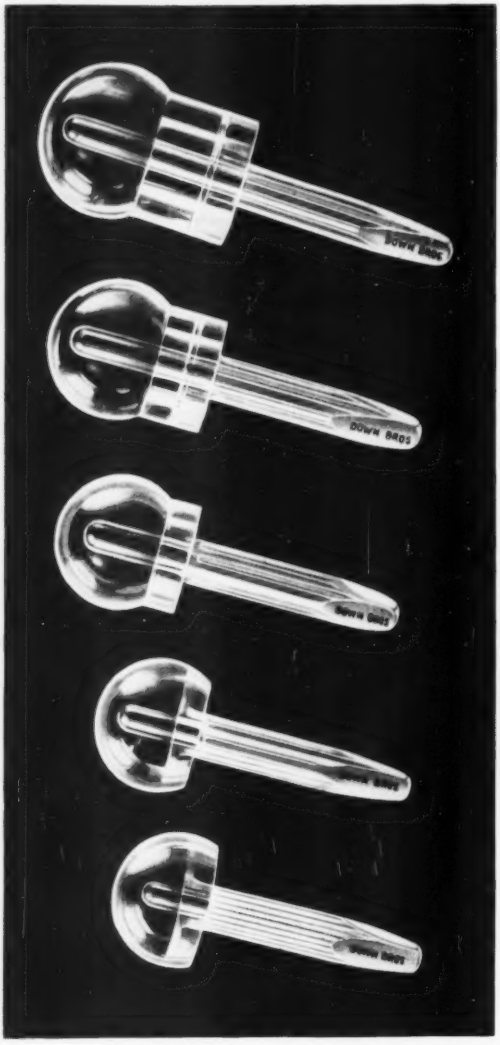

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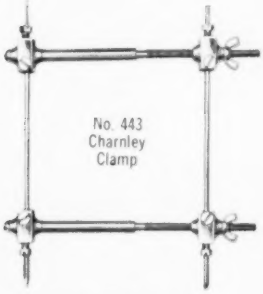

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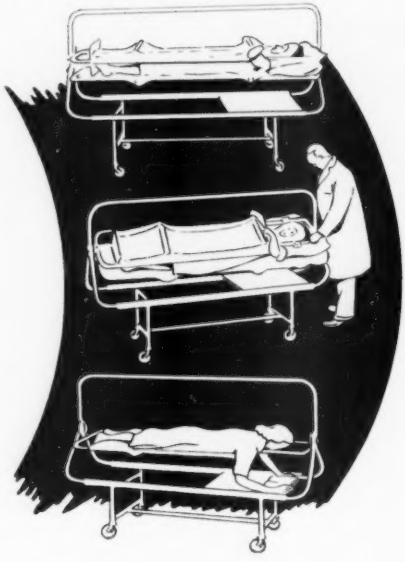

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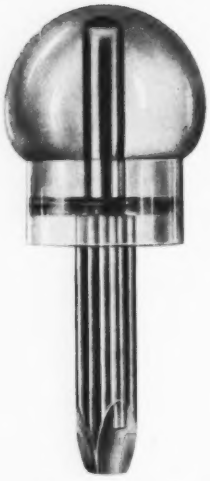

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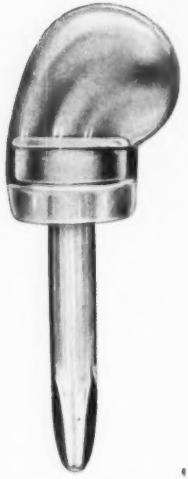

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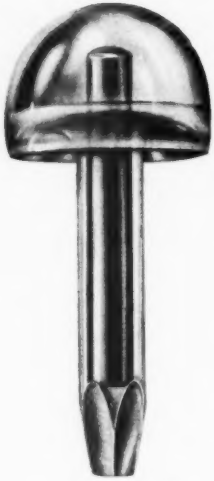

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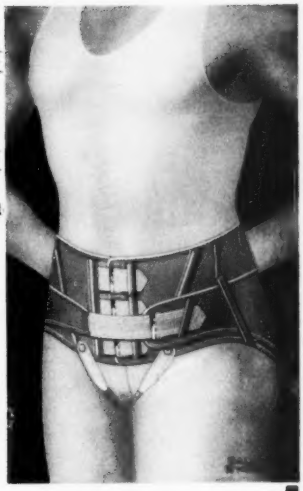

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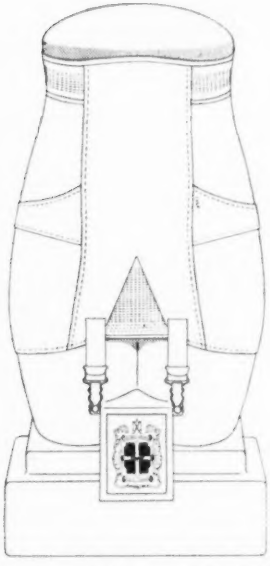

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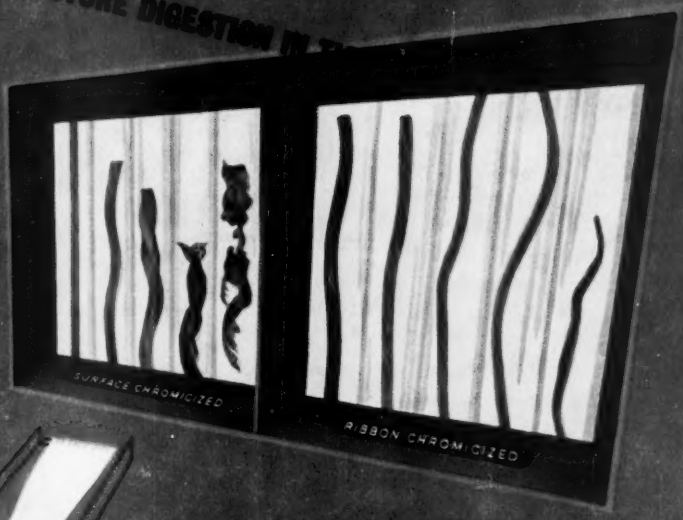

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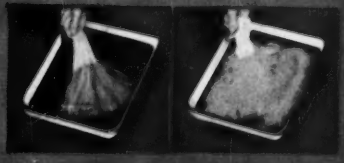

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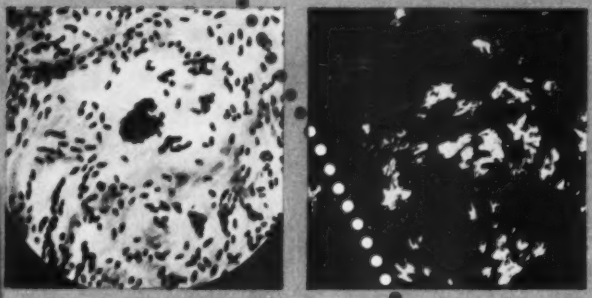

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We are also anxious to report the Proceedings of Colleges, Universities, Societies and Associations in every part of the world in so far as they contribute to the advance of orthopaedic surgery. A measure of international co-operation in publication has already been achieved and this will be fostered and, we hope, increased.

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